11.6.80

ISSN 0003-2999
vol. 59, no. 1 January 1980

5

# Anesthesia and Analgesia

UNIVERSITY COLLEGE OF MEDICINE
LIBRARY

**Journal of the International Anesthesia Research Society**

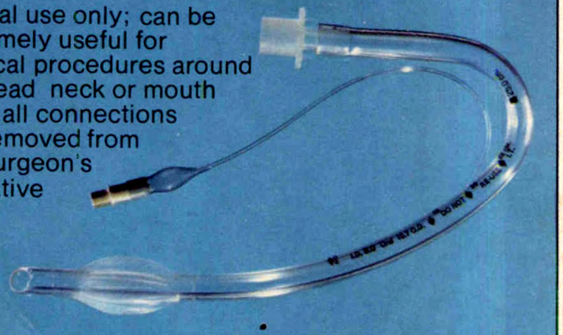
OLDEST PUBLICATION IN THE SPECIALTY–
ESTABLISHED 1922

# the problem solvers

## from National Catheter

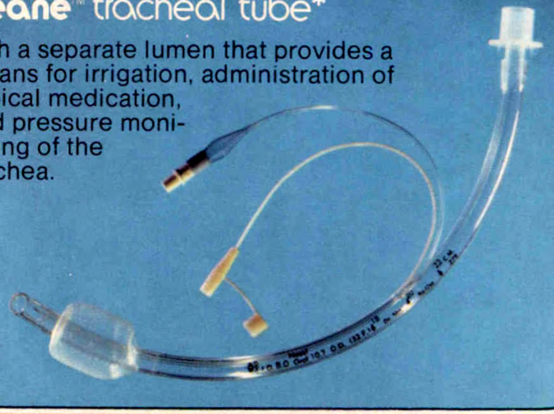
**RAE**™ cuffed, preformed tracheal tube*

for oral use only; can be extremely useful for surgical procedures around the head neck or mouth since all connections are removed from the surgeon's operative field.



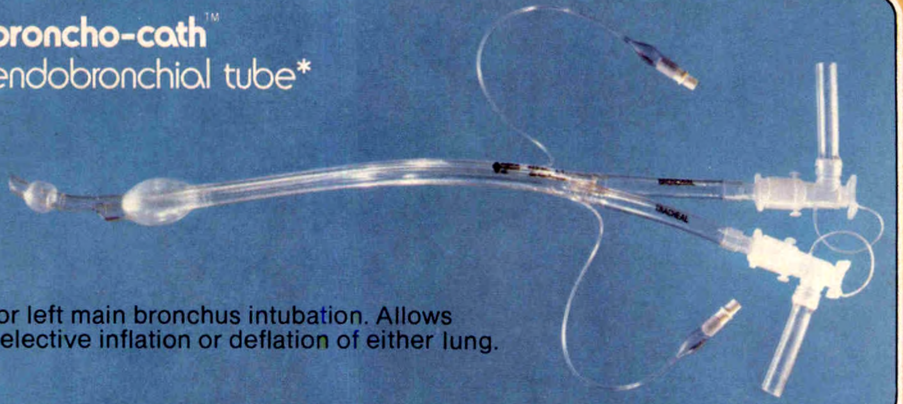
**deane**™ tracheal tube*

with a separate lumen that provides a means for irrigation, administration of topical medication, and pressure monitoring of the trachea.



**broncho-cath**™

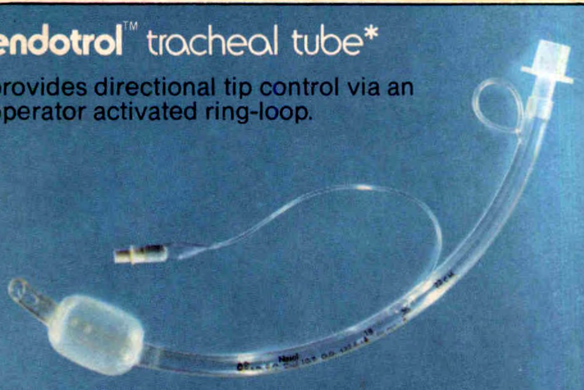
endobronchial tube*



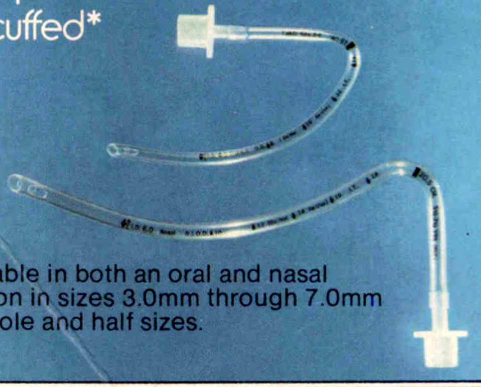
for left main bronchus intubation. Allows selective inflation or deflation of either lung.

**endotrol**™ tracheal tube*

provides directional tip control via an operator activated ring-loop.



**RAE**™ preformed tracheal tube -uncuffed*



available in both an oral and nasal version in sizes 3.0mm through 7.0mm in whole and half sizes.

Designed and manufactured by:

national catheter co.®
A DIVISION OF Mallinckrodt® INC.

Please send additional information on, "The problem solvers".
AA-18

NAME ______

ADDRESS ______

CITY ______ STATE ______

ZIP ______ PHONE ______

Cule -H04013-5 - P024576

P24576

Anesthesia and Analgesia

Journal of the
International Anesthesia Research Society

3645 Warrensville Center Road
Cleveland, Ohio 44122
Telephones (216) 295-1124, 295-1130

**EDITORIAL BOARD**

**Editor in Chief:**
**Nicholas M. Greene, M.D.,** New Haven, Connecticut

**Editors:**
**D. Ryan Cook, M.D.,** Pittsburgh, Pennsylvania
**Douglas B. Craig, M.D.,** Winnipeg, Manitoba
**E. Paul Didier, M.D.,** Rochester, Minnesota
**Ronald W. Dunbar, M.D.,** Atlanta, Georgia
**Alison B. Froese, M.D.,** Toronto, Ontario
**John P. Kampine, M.D.,** Milwaukee, Wisconsin
**David E. Longnecker, M.D.,** Charlottesville, Virginia
**John J. Savarese, M.D.,** Boston, Massachusetts
**N. Ty Smith, M.D.,** San Diego, California
**Robert K. Stoelting, M.D.,** Indianapolis, Indiana

**Book Review Editor:**
**E. Paul Didier, M.D.,** Rochester, Minnesota

**ANESTHESIA AND ANALGESIA** (ISSN 0003-2999) is published monthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, M.D., Bruce F. Cullen, M.D., E. Paul Didier, M.D., Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., B. B. Sankey, M.D., and Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris T. Nicholson, M.D., and T. H. Seldon, M.D.

**EDITORIAL CORRESPONDENCE** and manuscripts should be addressed to: **Nicholas M. Greene, M.D., Editor in Chief, Anesthesia and Analgesia, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: [203] 436-2887).** For information concerning preparation of manuscripts see "A Guide for Authors" published in each issue. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

**BOOKS FOR REVIEW** should be sent directly to the Book Review Editor, **E. Paul Didier, M.D., % Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55901.**

**REPRINTS:** For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

**BUSINESS CORRESPONDENCE,** including subscription and membership payments, single issue purchases, change of address notices, and requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122 (Telephones: [216] 295-1124, 295-1130).**

**SUBSCRIPTION RATES:** United States and U.S. possessions, $30.00 per year (12 issues); all other countries, $33.00.

**MEMBERSHIP DUES (Including Journal Subscription):** United States and U.S. possessions, $30.00 per year; all other countries, $33.00. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). **Educational Membership** (half the full price) available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only, upon completion of application including certification by applicant's program director.

**SINGLE ISSUES:** $5.50 each beginning 1979; $4.50 for years 1970–1978; $3.00 for years 1954–1969; $2.00 for years 1928–1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

**MAILING DATES:** Journals mailed 25th of month preceding issue date. Second class postage paid at Cleveland, Ohio and at additional mailing offices.

**CHANGE OF ADDRESS NOTICES:** Send to Cleveland business office as much in advance as possible to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable. POSTMASTER: Send address changes to Anesthesia and Analgesia, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

**ADVERTISING:** Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086 (Telephone: [609] 848-1000). Orders, contracts, and classified ad copy should be sent to the Cleveland office. Reproduction materials and inserts should be sent to Waverly Press, Inc., 300 Idlewild Avenue, Easton, Maryland 21601.

© 1980, International Anesthesia Research Society.

RSITY COLL EDICINI LIBRARY

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
1922

# Anesthesia and Analgesia

## EDITORIAL

Anesthesiology and Its Publications—Greene NM . . . 1

## SCIENTIFIC ARTICLES

A Computer-Assisted Preanesthesia Interview: Value of a Computer-Generated Summary of Patient's Historical Information in the Preanesthesia Visit—Tompkins BM, Tompkins WJ, Loder E, and Noonan AF . . . 3

Peripheral Vascular and Direct Effects of Digoxin in the Calf—Stanley TH, Lunn JK, Liu W-S, Gentry S, and Olsen D . . . 11

Withdrawal Convulsions in Mice following Nitrous Oxide—Harper MH, Winter PM, Johnson BH, Koblin DD, and Eger EI II . . . 19

Increased Skin Temperature during Transcutaneous Electrical Stimulation—Abram SE, Asiddao CB, Reynolds AC . . . 22

Cardiovascular and Neuromuscular Effects of Org NC 45, Pancuronium, Metocurine, and *d*-Tubocurarine in Dogs—Booij LHDJ, Edwards RP, Sohn YJ, and Miller RD . . . 26

Antagonism of Org NC 45 Neuromuscular Blockade by Neostigmine, Pyridostigmine, and 4-Aminopyridine—Booij LHDJ, van der Pol F, Crul JF, and Miller RD . . . 31

Maternal Halothane Anesthesia Reduces Cerebral Blood Flow in the Acidotic Sheep Fetus—Palahniuk RJ, Doig GA, Johnson GN, and Pash MP . . . 35

Percutaneous Cervical Central Venous Line Placement: A Comparison of the Internal and External Jugular Vein Routes—Belani KG, Buckley JJ, Gordon JR, and Castaneda W . . . 40

Ketamine Acts on the Peripheral Sympathetic Nervous System of Guinea Pigs—Juang MS, Yonemura K, Morioka T, and Tanaka I . . . 45

Intraocular Pressure during Enflurane and Neurolept Anesthesia in Adult Patients Undergoing Ophthalmic Surgery—Presbitero JV, Ruiz RS, Rigor BM, Drouilhet JH, and Reilly EL . . . 50

Furosemide Facilitates Recovery of Evoked Twitch Response after Pancuronium—Azar I, Cottrell J, Gupta B, and Turndorf H . . . 55

Physostigmine-Atropine Solution Fails to Reverse Diazepam Sedation—Garber JG, Ominsky AJ, Orkin FK, and Quinn P . . . 58

Detection of Fluorinated Anesthetic Metabolites by Sodium Fusion—Soltis JJ, and Gandolfi AJ . . . 61

# Contents

January 1980
Vol 59/Number 1

## CLINICAL REPORTS

**A Possible Hazard with Use of the Ohio Ēthrane Vaporizer**—Capan L, Ramanathan S, Chalon J, O'Meara JB, and Turndorf H . . . . . 65

**Persistent Electromechanical Cardiac Arrest following Administration of Cardioplegic and Glucose-Insulin-Potassium Solutions**—Kopman EA, Ramirez-Inawat RC . . . . . 69

**Spinal Subdural Hematoma Associated with Attempted Epidural Anesthesia and Subsequent Continuous Spinal Anesthesia**—Greensite FS, and Katz J . . . . . 72

**Intra-aortic Balloon Counterpulsation for Right Heart Failure**—Kopman EA, and Ramirez-Inawat RC . . . . . 74

**Severe Circulatory Shock following Protamine (An Anaphylactic Reaction)**—Moorthy SS, Pond W, and Rowland RG . . . . . 77

**Coma and Abnormal Neurologic Signs following Premedication**—Samuels SI, Washington E . . . . . 79

## LETTERS TO THE EDITOR

**Congenital Complete Heart Block**—Steward DJ, and Izukawa T . . . . . 81

**Obesity Supine Death Syndrome**—McKenzie R, and Wadhwa RK . . . . . 81

## BOOK REVIEWS

**Mechanisms of Pain and Analgesic Compounds**—Beers RF, and Bassett EG (Eds) . . 82

**Selected Papers in Respiratory Therapy, Second Edition**—DeKornfeld TJ . . . . . 82

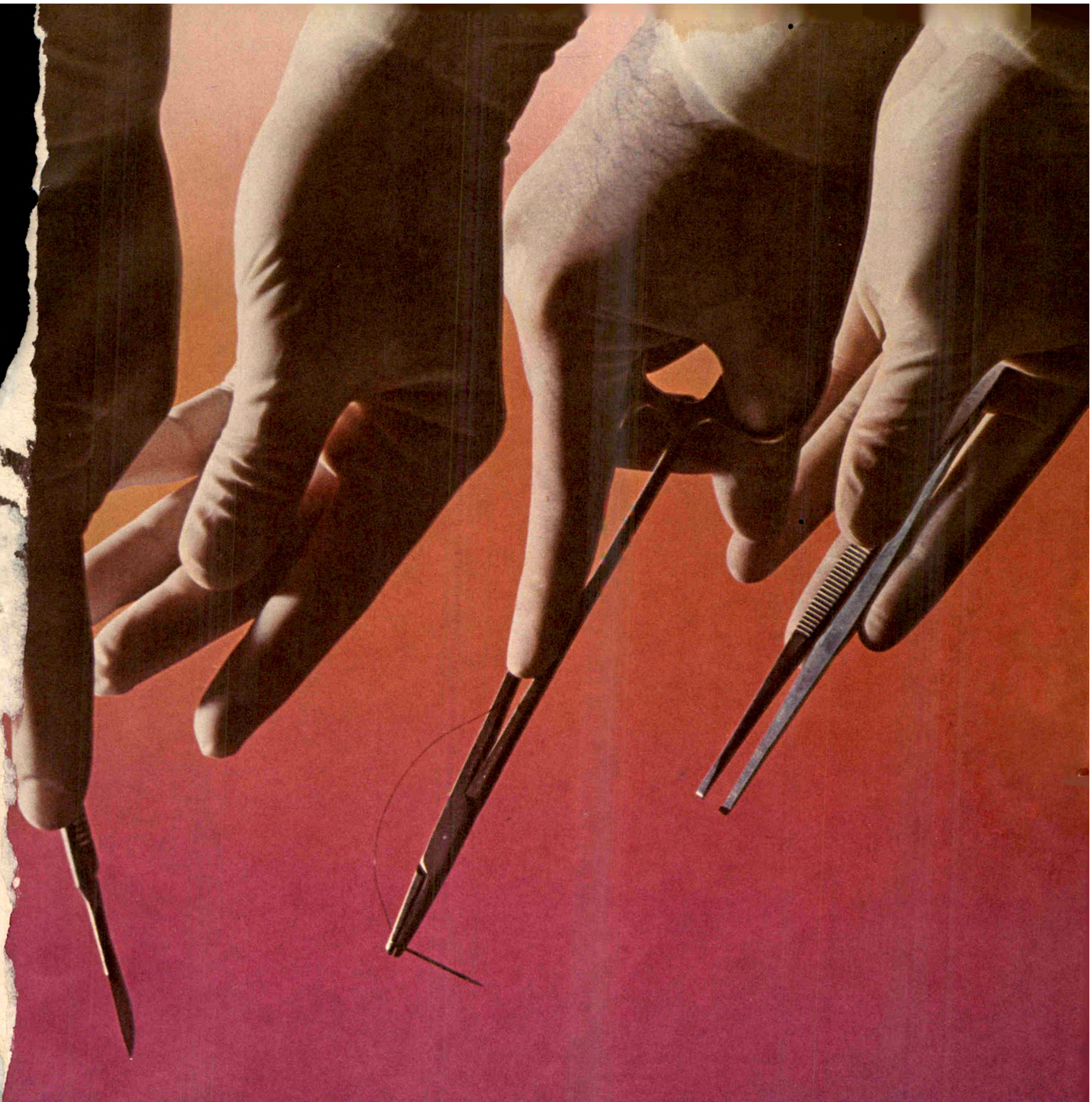
**Jamieson & Kay's Textbook of Surgical Physiology, Third Edition**—Ledingham IM, and MacKay C . . . . . 83

**Management of the Patient-Ventilator System: A Team Approach**—Martz KV, Jointer J, and Shepherd RM . . . . . 83

**Clinical Management of the Mother and Newborn**—Marx GF (Ed) . . . . . 84

**Monitoring Cerebral Function**—Prior PF . . . . . 84

Beginning
with intubation,
Proceeding
through surgery,
Until closure
Proceed with



Pavulon facilitates intubation and provides safe, neuromuscular blockade.

Histamine release and ganglionic blockade are rarely, if ever, seen[1]

Organon
A PART OF Akzona INC.

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# PAVULON®
pancuronium bromide

For a brief summary of prescribing information, please see the following page.

Until closure
**Proceed with PAVULON®**
pancuronium bromide
The clinically proven nondepolarizing muscle relaxant

**Brief Summary** (Please consult full package insert, enclosed in every package, before using Pavulon).

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

**CAUTION:** Federal law prohibits dispensing without prescription.

**Reference:**
1. Stanley and Liu, Anesth Analg 56 669, 1977

Organon
A PART OF AKZONA INC

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

## I.A.R.S. 1979 REVIEW COURSES

Booklet containing 14 Review Course Lectures given at 53rd Congress in March of 1979 is available from I.A.R.S. Cleveland business office at $5.00 per copy. Supply is limited and orders will be filled on basis of receipt date of order. Make checks payable to International Anesthesia Research Society and send with order.

.........................................................................

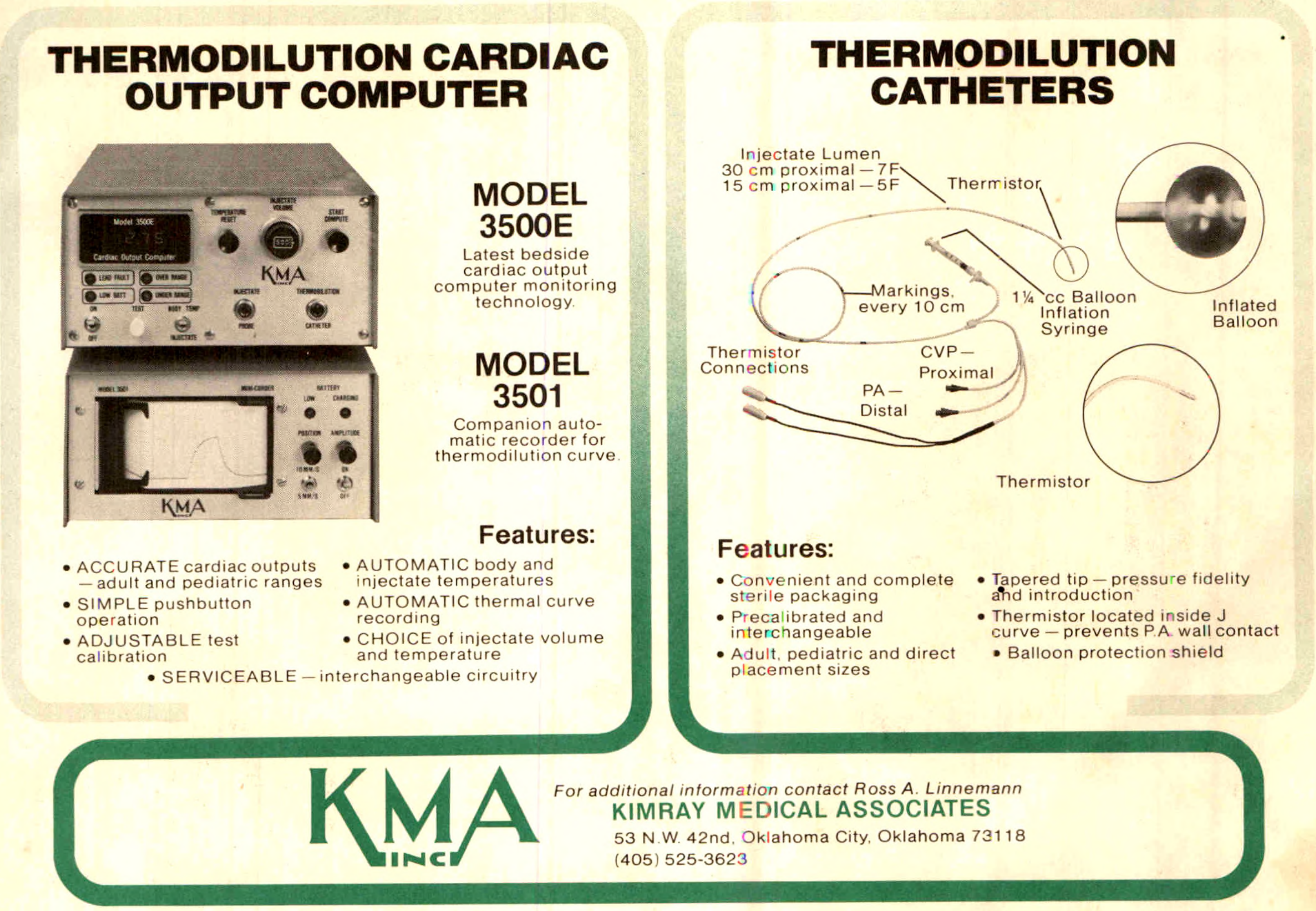
I.A.R.S.
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Enclosed is check for $________ for ________ copy(ies) of "1979 Review Course Lectures" to be sent to:

______________________________
(name)

______________________________
(Mail address)

__________ ____________________
(City-state-zip)



## THERMODILUTION CARDIAC OUTPUT COMPUTER

**MODEL 3500E**

Latest bedside cardiac output computer monitoring technology.

**MODEL 3501**

Companion automatic recorder for thermodilution curve.

**Features:**

- ACCURATE cardiac outputs — adult and pediatric ranges
- SIMPLE pushbutton operation
- ADJUSTABLE test calibration
- AUTOMATIC body and injectate temperatures
- AUTOMATIC thermal curve recording
- CHOICE of injectate volume and temperature
- SERVICEABLE — interchangeable circuitry

## THERMODILUTION CATHETERS

**Features:**

- Convenient and complete sterile packaging
- Precalibrated and interchangeable
- Adult, pediatric and direct placement sizes
- Tapered tip — pressure fidelity and introduction
- Thermistor located inside J curve — prevents P.A. wall contact
- Balloon protection shield

KMA INC

*For additional information contact Ross A. Linnemann*
**KIMRAY MEDICAL ASSOCIATES**
53 N.W. 42nd, Oklahoma City, Oklahoma 73118
(405) 525-3623

# INTERNATIONAL SYMPOSIUM ANESTHESIA AND THE HEART PATIENT

**May 30, 31 & June 1, 1980** ***sponsored by*** **The Cleveland Clinic Foundation**

The Symposium is a singular gathering of distinguished scientists. It will provide a comprehensive review of current experience, recent advances and challenges of the future.

## TOPICS

*Pathophysiology of heart disease
*Perioperative diagnosis and intraoperative monitoring
*Anesthesia for open heart surgery
*Postoperative care
*Hemodynamic effects of anesthetic drugs
*Anesthesia for noncardiac operations in patients with heart disease
*Pharmacological and mechanical support of the circulation

## INTERNATIONAL FACULTY

A. Baraka
F. Belojartsev
H. Benzer
M. Boulanger
P. Foex
A. Gilston
E. Moffitt
D. Stewart
K. Sykes
E. Wynands

## AMERICAN FACULTY

A. Boutros
D. Bregman
A. Breuer
G. DeBoer
N. Ellison
A. El-Etr
F. Estafanous
K. Garman
M. Chattas
J. Gravenstein
G. Gregory
W. Hamilton
J. Kampine
J. Kaplan
A. Keats
M. Laver
W. Lell
E. Lowenstein
F. Loop
P. Maroko
R. Merin
A. Romagnoli
J. Schauble
J. Schweiss
W. Sheldon
G. Silvay
M. Sones
E. Stanley
N. Starr
W. Stevens
R. Stoelting
R. Tarazi
S. Tarhan
D. Vidt
R. White
A. Zurick

For registration and information, contact the International Symposium Office, The Cleveland Clinic Educational Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106 (216) 444-5696. Registration fee of $275 includes panels, luncheons, and banquet.

Announcing...
Vaporizer interlock
for Foretrend 100 and
300 Anesthesia Machines
FOREGGER.

...a name you can trust for your anesthesia equipment needs.

- Anesthesia Gas Machines
- $CO_2$ Absorbers
- Vaporizers
- Anesthesia Ventilators
- Oxygen Monitors
- Pressure Monitors
- Laryngoscopes
- Tube Connectors and Adapters
- Intubation Accessories
- Endotracheal Tubes
- Anesthesia Masks and Breathing Bags
- Anesthesia Breathing Circuits, Disposable and Reusable
- Bacteria Filters
- Oral and Naso Pharyngeal Airways, Disposable and Reusable
- Hose Assemblies and Fittings
- Suction Administering Equipment, Disposable and Reusable

FOREGGER... NOW A DIVISION OF
THE PURITAN-BENNETT CORPORATION.

PURITAN-BENNETT CORPORATION
FOREGGER
MEDICAL DIVISION

Puritan-Bennett Corporation
Foregger Medical Division
835 Wheeler Way
Langhorne, PA 19047

# CORTICOID THERAPY IN CRITICAL CARE

Pharmacologic doses of corticoids have been used in the treatment of shock unresponsive to conventional therapy, if adrenocortical insufficiency exists or is suspected.

## Differences That Count

Hexadrol® phosphate injection is easy to handle, store and administer. Already in solution, it can be used directly from the vial. Hexadrol has benzyl alcohol as a preservative and is stable at room temperature.

The multi-dose vial minimizes waste. When used in pharmacologic doses, Hexadrol offers significant savings over methylprednisolone.*

# Hexadrol® Phosphate Injection

## dexamethasone sodium phosphate injection USP

**BEFORE PRESCRIBING OR ADMINISTERING, PLEASE CONSULT COMPLETE PRODUCT INFORMATION, A SUMMARY OF WHICH FOLLOWS:**

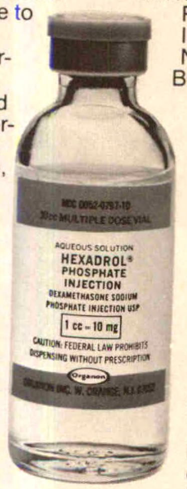
**ACTIONS**—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

**CONTRAINDICATIONS**—Systemic fungal infections—Hypersensitivity to any component.

**WARNINGS**—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

**Usage In Pregnancy.** Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be necessary.



100 mg

All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

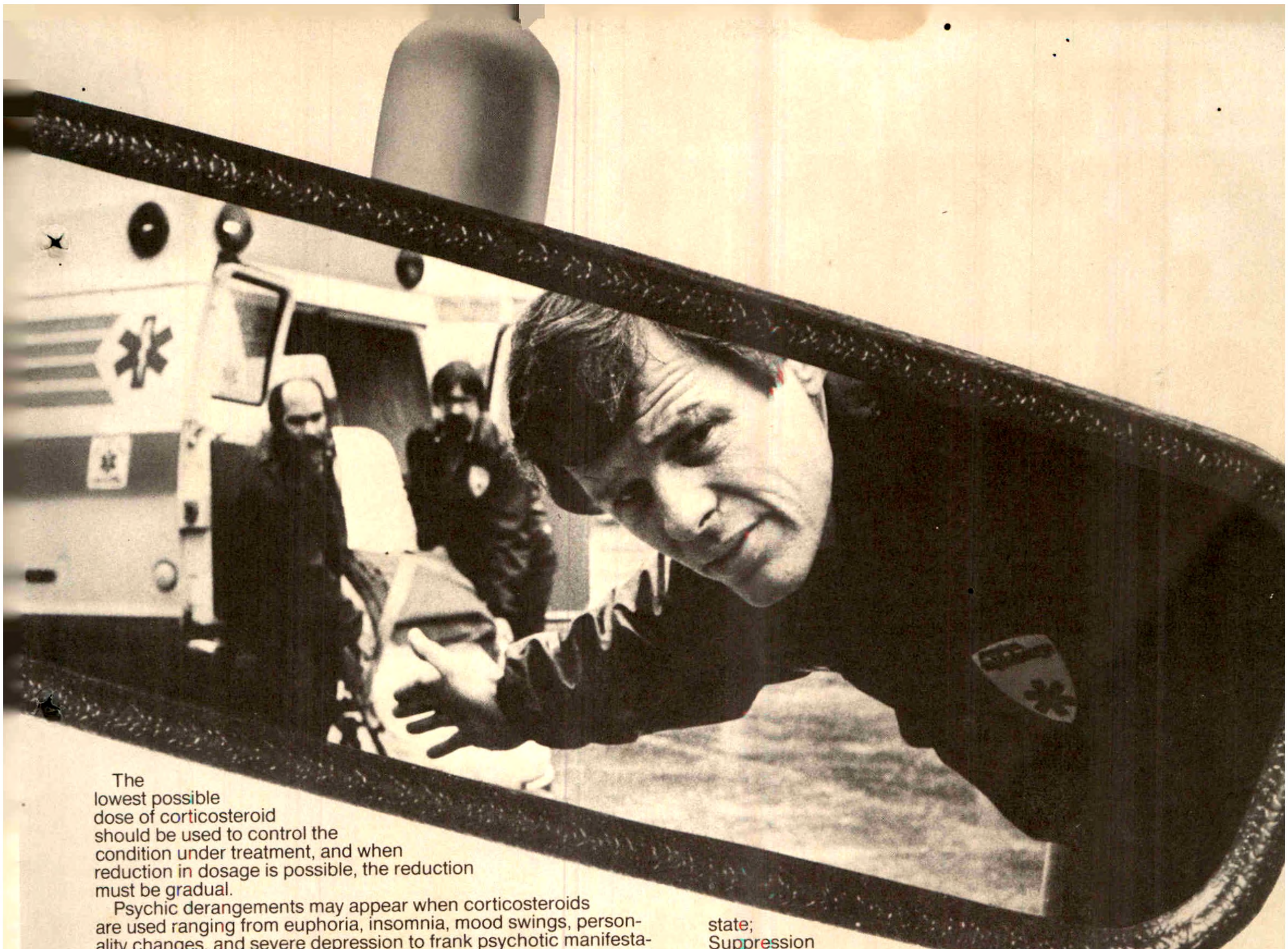
**PRECAUTIONS**—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

---

*Based on average wholesale price listings in *Drug Topics Red Book 1979*. Actual prices paid by direct purchasers will vary by order size but are usually lower for Hexadrol.



The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, approrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

**ADVERSE REACTIONS—**

**Fluid and electrolyte disturbances:** Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

**Musculoskeletal:** Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

**Gastrointestinal:** Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

**Dermatologic:** Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

**Neurological:** Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

**Endocrine:** Menstrual irregularities; Development of Cushingoid state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; Increased requirements for insulin or oral hypoglycemic agents in diabetics.

**Ophthalmic:** Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

**Metabolic:** Negative nitrogen balance due to protein catabolism.

**Miscellaneous:** Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

**DOSAGE AND ADMINISTRATION**—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

**DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.**

**CAUTION**—Federal law prohibits dispensing without prescription.

**HOW SUPPLIED**—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25; 10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

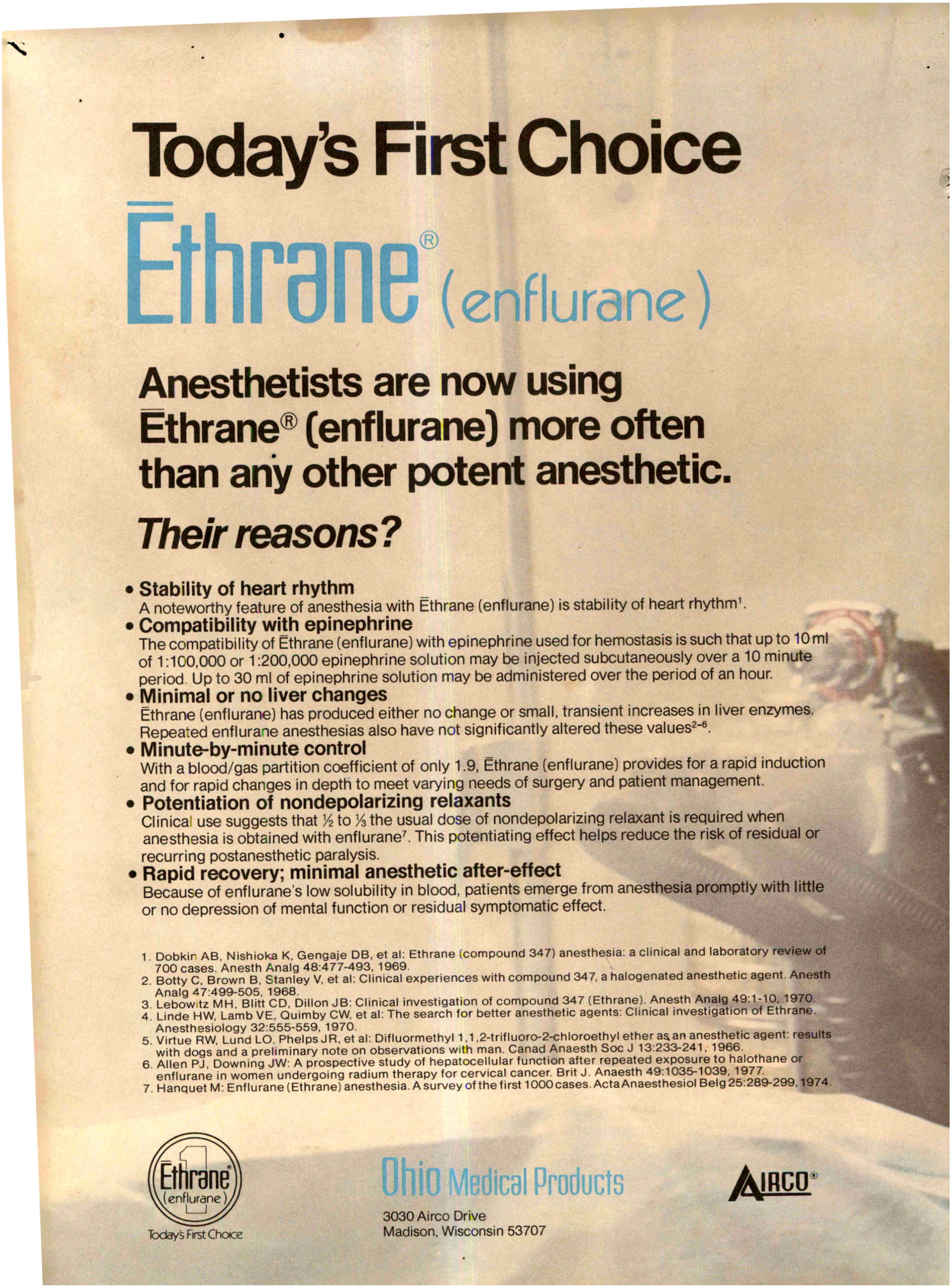
Hexadrol is available in two potencies, 4mg/cc and 10mg/cc in aqueous solution with 1% benzyl alcohol as preservative.

**When You Need it... Hexadrol Has It!**

Organon

A PART OF Akzona INC.

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052



# Today's First Choice

# Ēthrane® (enflurane)

## Anesthetists are now using Ēthrane® (enflurane) more often than any other potent anesthetic.

## *Their reasons?*

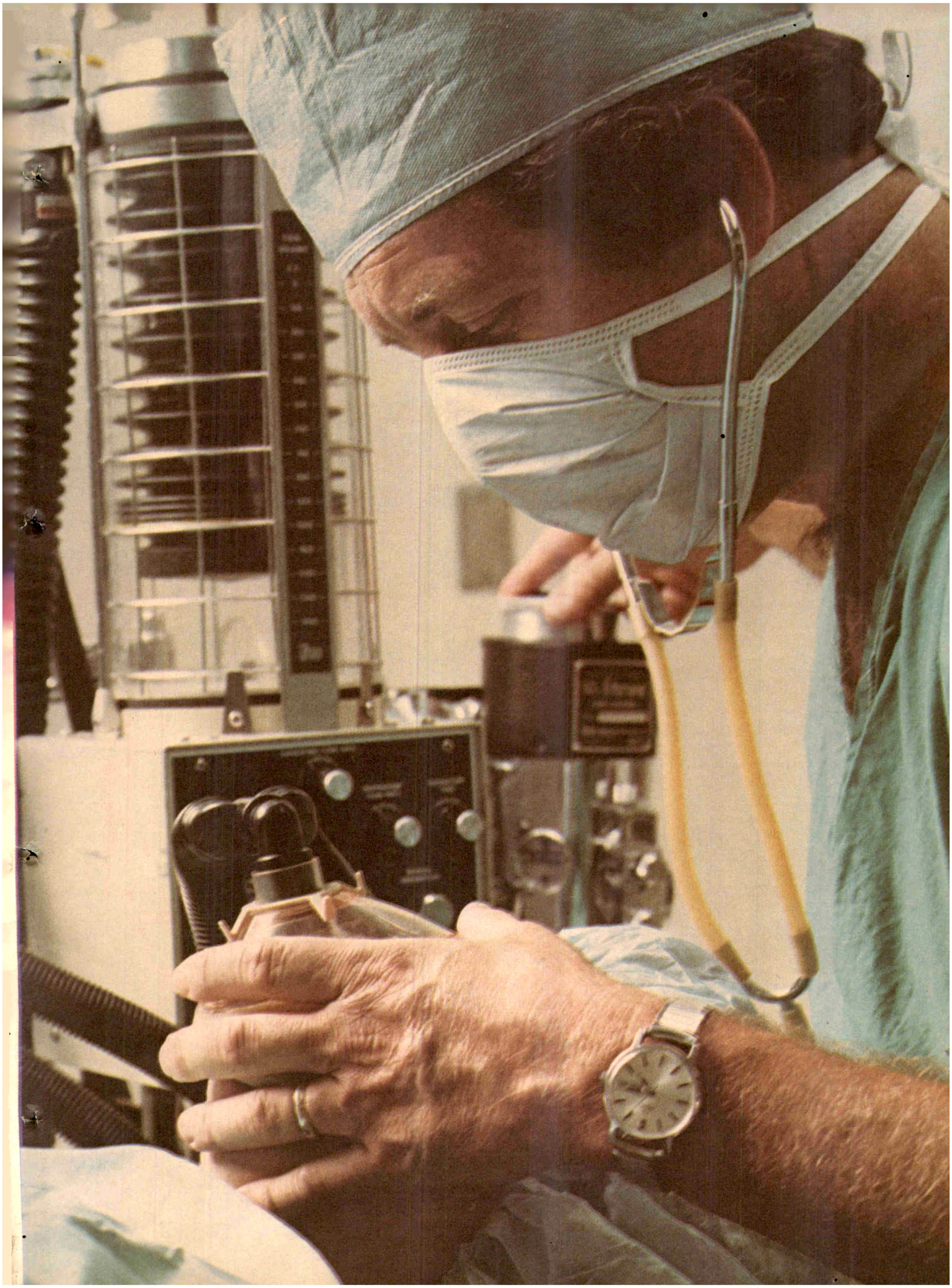
- **Stability of heart rhythm**
  A noteworthy feature of anesthesia with Ēthrane (enflurane) is stability of heart rhythm[1].
- **Compatibility with epinephrine**
  The compatibility of Ēthrane (enflurane) with epinephrine used for hemostasis is such that up to 10 ml of 1:100,000 or 1:200,000 epinephrine solution may be injected subcutaneously over a 10 minute period. Up to 30 ml of epinephrine solution may be administered over the period of an hour.
- **Minimal or no liver changes**
  Ēthrane (enflurane) has produced either no change or small, transient increases in liver enzymes. Repeated enflurane anesthesias also have not significantly altered these values[2-6].
- **Minute-by-minute control**
  With a blood/gas partition coefficient of only 1.9, Ēthrane (enflurane) provides for a rapid induction and for rapid changes in depth to meet varying needs of surgery and patient management.
- **Potentiation of nondepolarizing relaxants**
  Clinical use suggests that ½ to ⅓ the usual dose of nondepolarizing relaxant is required when anesthesia is obtained with enflurane[7]. This potentiating effect helps reduce the risk of residual or recurring postanesthetic paralysis.
- **Rapid recovery; minimal anesthetic after-effect**
  Because of enflurane's low solubility in blood, patients emerge from anesthesia promptly with little or no depression of mental function or residual symptomatic effect.

1. Dobkin AB, Nishioka K, Gengaje DB, et al: Ethrane (compound 347) anesthesia: a clinical and laboratory review of 700 cases. Anesth Analg 48:477-493, 1969.
2. Botty C, Brown B, Stanley V, et al: Clinical experiences with compound 347, a halogenated anesthetic agent. Anesth Analg 47:499-505, 1968.
3. Lebowitz MH, Blitt CD, Dillon JB: Clinical investigation of compound 347 (Ethrane). Anesth Analg 49:1-10, 1970.
4. Linde HW, Lamb VE, Quimby CW, et al: The search for better anesthetic agents: Clinical investigation of Ethrane. Anesthesiology 32:555-559, 1970.
5. Virtue RW, Lund LO, Phelps JR, et al: Difluormethyl 1,1,2-trifluoro-2-chloroethyl ether as an anesthetic agent: results with dogs and a preliminary note on observations with man. Canad Anaesth Soc J 13:233-241, 1966.
6. Allen PJ, Downing JW: A prospective study of hepatocellular function after repeated exposure to halothane or enflurane in women undergoing radium therapy for cervical cancer. Brit J. Anaesth 49:1035-1039, 1977.
7. Hanquet M: Enflurane (Ethrane) anesthesia. A survey of the first 1000 cases. Acta Anaesthesiol Belg 25:289-299, 1974.

Ēthrane® (enflurane)
Today's First Choice

Ohio Medical Products
3030 Airco Drive
Madison, Wisconsin 53707

AIRCO®

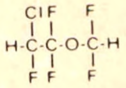


# Ēthrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

## DESCRIPTION

ĒTHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$H-\underset{F}{\overset{Cl}{C}}-\underset{F}{\overset{F}{C}}-O-\underset{F}{\overset{F}{C}}-H$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \qquad A = 7.967$$
$$B = -1678.4$$
$$T = {}^{\circ}C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ĒTHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ĒTHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ĒTHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

## ACTIONS

ĒTHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ĒTHRANE are rapid. ĒTHRANE has a mild sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ĒTHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ĒTHRANE. ĒTHRANE reduces ventilation as depth of anesthesia increases. High $pCO_2$ levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ĒTHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ĒTHRANE anesthesia. ĒTHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ĒTHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ĒTHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ĒTHRANE.

Biotransformation of ĒTHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ĒTHRANE anesthesia in man in the absence of surgery. Thus ĒTHRANE does not depress this aspect of the immune response.

## INDICATIONS

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

## CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.

## WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ĒTHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ĒTHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ĒTHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

## PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ĒTHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ĒTHRANE.

## ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

## DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

- a) vaporizers calibrated specifically for ĒTHRANE;
- b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ĒTHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

**Induction:** Induction may be achieved using ĒTHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ĒTHRANE mixture. In general, inspired concentrations of 3.5-4.5% ĒTHRANE produce surgical anesthesia in 7-10 minutes.

**Maintenance:** Surgical levels of anesthesia may be obtained with 1.5-3% ĒTHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ĒTHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

**Overdosage:** In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

## PACKAGING

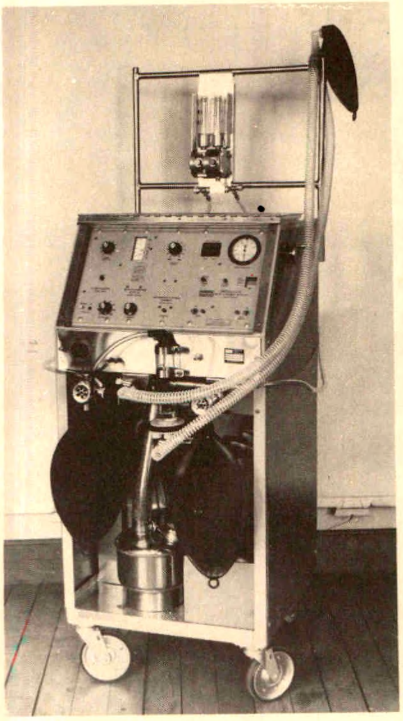
ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

**Ohio Medical Products**
Division of Airco Inc.
P.O. Box 7550, 3030 Airco Drive, Madison, Wis. 53707

AIRCO®

# EMERSON IMV Ventilator

## Intermittent Mandatory Ventilation



Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

## VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of $CO_2$ rise, as noted by Kirby and associates.[1]

## VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

*Please request Form 3-MV.*

**J. H. EMERSON COMPANY**
**CAMBRIDGE, MASSACHUSETTS 02140**

# ANTILIRIUM

## (Physostigmine Salicylate)

**QUICKLY BECOMING THE DRUG OF CHOICE FOR REVERSING PROLONGED SOMNOLENCE, DELIRIUM AND OTHER ANTICHOLINERGIC SIDE EFFECTS.**

More Anesthesiologists are relying on ANTILIRIUM because...

- Patients are revived in minutes after I.V. administration.
- Reverses anticholinergic side effects.
- Patient safety—metabolized in the body in 60 to 120 minutes.

ONE DOZEN
2 ml. AMPULES
ANTILIRIUM
(Physostigmine Salicylate)
Each ml. contains:
PHYSOSTIGMINE SALICYLATE 1 mg
In a vehicle composed of Sodium Bisulfite 0.1%, Benzyl Alcohol 2.0%, in water for injection q.s.
CAUTION: Federal law prohibits dispensing without prescription.
OJ &F
O'NEAL, JONES & FELDMAN
A DIVISION OF CHROMALLOY PHARMACEUTICAL, INC.
ST. LOUIS, MISSOURI 63043
PROTECT FROM LIGHT
ANTILIRIUM (Physostigmine Salicylate)

**ANTILIRIUM CROSSES THE BLOOD BRAIN BARRIER WHEREAS NEOSTIGMINE DOES NOT**

ANTILIRIUM, unlike other anticholinesters including neostigmine does not have a quaternary nitrogen atom, but has a tertiary amine. For this reason it is nonionized and rapidly crosses the blood brain barrier.

OJ &F O'NEAL, JONES & FELDMAN PHARMACEUTICALS • ST. LOUIS, MO 63043

**ANTILIRIUM**
**(Physostigmine Salicylate)**

**DESCRIPTION**: ANTILIRIUM Injection (physostigmine salicylate) is OJF's brand of physostigmine salicylate.

ANTILIRIUM INJECTION 1 mg./ml.
FOR INTRAMUSCULAR OR INTRAVENOUS USE
Each ml. contains:
PHYSOSTIGMINE SALICYLATE 1 mg.
In a vehicle composed of Sodium Bisulfite 0.1%, Benzyl Alcohol 2.0%; in water for injection q.s.

**ACTION**: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. The action of acetylcholine is normally very fleeting because of its hydrolysis by a specific enzyme. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine. The changes in body function which are produced by the injection of physostigmine are, therefore, very similar to those which would occur from simultaneous stimulation of the parasympathetic nerves and include contraction of the pupil, increased tonus of the intestinal musculature, constriction of the bronchi and stimulation of secretion of the salivary and sweat glands.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quarternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Drugs with anticholinergic properties primarily antagonize acetylcholine competitively at the neuroreceptor site. Cardiac muscle, exocrine glands, and smooth muscle are most markedly affected. Action of the inhibitors is overcome by increasing the level of acetylcholine naturally generated in the body through inhibiting the enzyme (cholinesterase) which normally prevents accumulation of excess acetylcholine. It does this by hydrolyzing that compound to inactive acetic acid and choline. Agents which inhibit this enzyme, so that acetylcholine accumulates at the neuroreceptor sites, are called anticholinesterases.

Physostigmine, one of the anticholine esterases which is a tertiary amine, crosses into the central nervous system and can reverse both central and peripheral anticholinergic actions.

The anticholinergic syndrome has both central and peripheral signs and symptoms. Central toxic effects include anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Severe poisoning may produce coma, medullary paralysis, and death. Peripheral toxicity is characterized by tachycardia, hyperpyrexia, mydriasis, vasodilatation, urinary retention, diminution of gastrointestinal motility, decrease of secretion in salivary and sweat glands, and loss of secretions in the pharynx, bronchi, and nasal passages.

Some drugs in the anticholinergic group, such as imipramine and related tricyclics also produce additional toxic effects such as cardiac arrhythmias which can be reversed by physostigmine.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Toxic effects from mixed drug ingestions and combination preparations such as amitriptyline and perphenazine may respond less dramatically. Since physostigmine is rapidly metabolized, therapeutic doses may be necessary at intervals as life-threatening signs such as arrhythmias, convulsions, and deep coma recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

**INDICATIONS**: **TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.**

It has also been reported that ANTILIRIUM (physostigmine salicylate) may antagonize the CNS depressant effects of diazepam.

**CONTRAINDICATIONS**: Physostigmine salicylate injections should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents (decamethonium, succinylcholine).

**WARNING**: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions. An overdosage of ANTILIRIUM can cause a cholinergic crisis.

**PRECAUTIONS**: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is antagonist and antidote for physostigmine.

**ADMINISTRATION AND DOSAGE**: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur. Physostigmine salicylate is rapidly metabolized in the body.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: Ampuls, 2 ml. packed 12 per box.

OJ &F **O'NEAL, JONES & FELDMAN**
**ST. LOUIS, MISSOURI 63043**

1079

# ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA, effective

________________________________

________________________________

**From**—(Current or former address)

________________________________

Street Address

________________________________

City, State, Zip Code

**Important: Show your name and address exactly as your Journal is now addressed.**

________________________________

**To**—(New Address)

________________________________

Street Address

________________________________

City, State, Zip Code

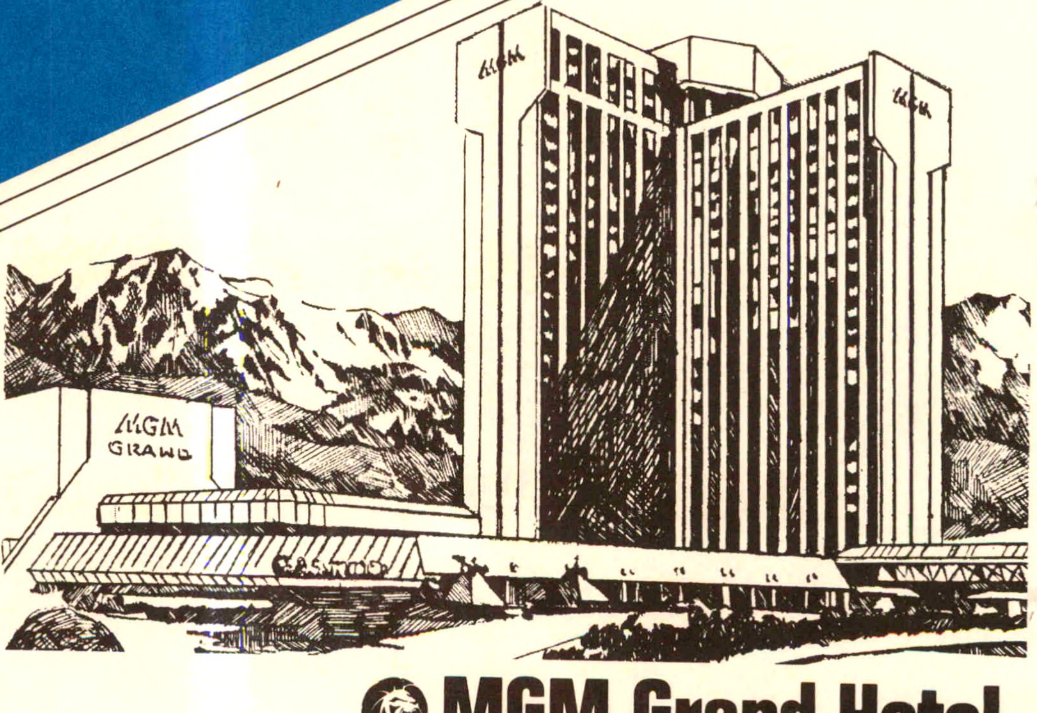
________________________________

Print Your Name

# 54th Congress

March 9-13, 1980

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY



## MGM Grand Hotel
## Reno, Nevada

## 54th CONGRESS MEETING SCHEDULE

*SUNDAY, MARCH 9th:*

Registration: 1–7 p.m.
Exhibits: 1–5 p.m.
"The Keys of Paradise" (NOVA movie on endorphins): 3–4 p.m.
Complimentary Informal Reception: 6–7 p.m.

*MONDAY, MARCH 10th through THURSDAY, MARCH 13th:*

*Registration:* Daily, coinciding with scientific meeting hours.

*Scientific Program:* Monday: 8:30–4:30 p.m.
Tuesday: 8 a.m.–4:30 p.m.
Wednesday: 8 a.m.–12 Noon (FREE AFTERNOON)
Thursday: 8 a.m.–4:15 p.m.

...A total of 62 scientific papers and 16 Review Course Lectures will be offered in concurrent sessions throughout the 3½ day scientific meeting.

...The Becton-Dickinson and Baxter/Travenol Lectures will be given at single•sessions at 1:30 p.m. on Monday and Tuesday.

(NOTE: A booklet including the 16 Review Course Lectures and abstracts of the 62 papers will be given to attendees as part of their registration. After the meeting this will be available for sale to others through the Cleveland business office at $5 per copy.)

*Scientific and Technical Exhibits:* In addition to the Sunday exhibit viewing hours, exhibits will be open from 10 a.m. to 5 p.m. on Monday and Tuesday; and from 8 a.m. to 12 noon on Wednesday.

## REGISTRATION FEES

| | *Paid by March 3* | *At Meeting* |
|---|---|---|
| IARS Members, Associate Members | $75.00 | $85.00 |
| IARS Educational Members | NO FEE | NO FEE |
| Non-Members | $125.00 | $135.00 |
| * New Members | $100.00 | $110.00 |
| ** Non-Members (residents, nurse trainees) | $20.00 | $20.00 |
| *** New Members (residents, nurse trainees) | $30.00/$45.00 | $30.00/$45.00 |

* with membership application
** with letter from program director
*** with completed application; $30 for 2-yr., $45 for 3-yr. membership

## CONTINUING EDUCATION CREDITS

**American Medical Association:** This Continuing Medical Education offering meets the criteria for 22 hours of Category 1 credit for the Physicians Recognition Award of the A.M.A.

**American Association of Nurse Anesthetists:** Prior approval pending for 22 AANA continuing education credits.

## PRE-REGISTRATION MATERIAL, HOTEL CARD, PROGRAM

Registration material will be sent in mid-December to all IARS members, associate members and educational members.

IARS members and others outside of the United States who wish to attend the meeting should advise Cleveland office so that another set of material can be sent airmail.

# IARS 54th CONGRESS DISTINGUISHED LECTURERS

---

## Fifteenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture

Monday, March 10, 1980

**"Recent Advances in the Study of the Control of Breathing"**

**Joseph Milic-Emili, M.D.**
*Professor, Department of Physiology*
*Professor, Experimental Medicine*
McGill University, Montreal, Quebec, Canada
*Director, Meakins Christie Laboratories,*
Montreal, Quebec, Canada
*Former Chairman, Department of Physiology*
McGill University, Montreal

Dr. Milic-Emili's major research interests in respiratory physiology concern mechanics of breathing, pulmonary gas exchange and distribution, ventilation and perfusion relationships in the lungs, and the control of breathing.

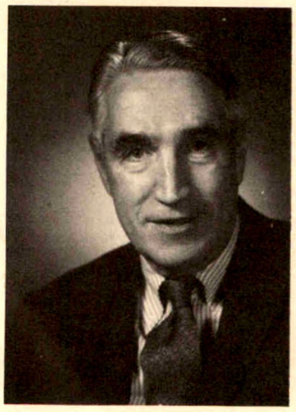
---

## Eighteenth Annual Baxter/Travenol Lecture

Tuesday, March 11, 1980

**"Evolution of Instrumentation and Technics for the Study of Cardiovascular Dynamics"**

**Earl Howard Wood, M.D., Ph.D.**
*Senior Consultant, Biodynamics Research Unit*
Department of Physiology & Biophysics
Mayo Foundation, Rochester, Minnesota
*Professor of Physiology and Medicine*
Mayo Medical School, Rochester, Minnesota



Dr. Wood's research goal has been the achievement of better understanding of the mechanisms by which the human heart, lungs and circulation adapt to the stress of disease, exercise or altered gravity.

CP24,576

# EDITORIAL

# Anesthesiology and Its Publications

AFTER being published for the last 58 years as a bimonthly journal, ANESTHESIA AND ANALGESIA now goes to monthly publication with this, the January 1980, issue. The reason for this change is simply that the amount of material submitted to us which merits publication has increased to the point where it can no longer be accommodated on a bimonthly basis. This tells us, we believe, something about where we stand in anesthesiology today, something best appreciated when this rather modest change is put into the context of what has happened in the field of anesthesia publications since anesthesia was first introduced in 1846.

Anesthesia was widely and extensively practiced in the years after 1846. There were, however, no journals devoted to matters anesthetic for almost 70 years. Nor, in retrospect, was there probably any need for anesthetic journals during this time. The number of physicians full-time in anesthesia was, at least outside the United Kingdom, miniscule. Those who were on the scene were practicing anesthesia with such vigor and dedication they had little time for or interest in research or publication. The first "journal" to be devoted to anesthesia, *The American Journal of Anesthesia and Analgesia*, did not appear until 1914. Published as a quarterly supplement to *The American Journal of Surgery*, it had as its sponsors the American Association of Anesthetists and the Scottish Society of Anaesthetists. It also had as its guiding light one of the most dynamic and fascinating of the early pioneers in American anesthesia, Dr. Francis H. McMechan. Dr. McMechan ultimately and, probably, inevitably found the step-child arrangement with *The American Journal of Surgery* somewhat less than satisfying to one with his drive and ambition to improve the status of anesthesia. He therefore started in 1922 the publication of a bimonthly competing journal, *Current Researches in Anesthesia and Analgesia*. The latter proved so popular and so successful that publication of *The American Journal of Anesthesia and Analgesia* was terminated in 1926. *Current Researches in Anesthesia and Analgesia* (its name was changed to *Anesthesia and Analgesia, Current Researches* in 1957 and to ANESTHESIA AND ANALGESIA in 1979) is thus the oldest journal in anesthesia in the world. *Current Researches in Anesthesia and Analgesia* had as its initial sponsor the National Anesthesia Research Society. One of the original objectives of the journal was to provide a more effective mechanism for publication of the Transactions of the Associated Anesthetists of the United States and Canada, an organization which included the Canadian Society of Anesthetists (which became the section of Anaesthesia of the Canadian Medical Association in 1927), the Interstate Society of Anesthetists (everything East of the Mississippi and North of the Mason-Dixon line), the Southern Association of Anesthetists, the Mid-Western and Pacific Coast Associations of Anesthetists, and the American Association of Anesthetists. In 1925 the National Anesthesia Research Society changed its name to the International Anesthesia Research Society, the organization that has continued to publish the journal through its changes in name. The flavor, background, and history of anesthesia in the United States is nowhere more readily and richly appreciated than by scanning early issues of *Current Researches in Anesthesia and Analgesia.*

*Current Researchs in Anesthesia and Analgesia* was but a harbinger of things to come. Within a year the first issue of the *British Journal of Anaesthesia* appeared. It was originally published in hopes of serving as a focal point for the organization of all regional anesthesia societies in the United Kingdom, and, eventually, regional societies in all "dominions, colonies and dependencies" into a single British Association of Anaesthetists. This goal was never realized, but the journal has continued to prosper, first quarterly, and since 1955, as a monthly publication.

The Association of Anaesthetists of Great Britain and Ireland, founded in 1932, was the organization which ultimately amalgamated all the regional anesthesia societies in the United Kingdom into one association. In 1946 it started publishing its own journal, *Anaesthesia*, quarterly at first but bimonthly since 1973.

COLLEGE OF [illegible] LIBRARY [illegible]ERSITY [illegible] N

# EDITORIAL

*Anesthesiology* first appeared in 1940 as the bimonthly publication of the American Society of Anesthetists. Parented by the New York Society of Anesthetists in 1936, which in turn evolved from the Long Island Society of Anesthetists (founded in 1905), the A.S.A. became the American Society of Anesthesiologists in 1945. The A.S.A. and the specialty continued to grow and prosper over the years. By 1969 *Anesthesiology* was obliged to convert to monthly publication to accommodate the ever increasing volume of material being written in the field.

Yet another new anesthesia journal appeared shortly after *Anesthesiology* when, in 1944, *Anésthesie et Analgésié*, the journal of La Société Française d'Anesthésie et d'Analgésie, started as a bimonthly publication. *Reanimation* was added to its name and to that of its sponsoring society in 1957. This, the French journal of anesthesia, was in turn followed by another continental anesthesia journal in 1952, when *Der Anaesthesist* first appeared as a bimonthly publication of the Österreichischen Gesellschaft für Anaesthesiologie. By 1958, when European anesthesia had grown to such an extent that *Der Anaesthesist* became a monthy journal, its sponsors also included the German and Swiss anesthesia societies.

Yet another, a third, North American anesthesia journal, the *Canadian Anaesthetists' Society Journal*, appeared on the scene in 1954 as the bimonthly publication of the Canadian Anaesthetists' Society. A third European journal also started publication soon thereafter. *Acta Anaesthesiologica Scandinavica*, the journal of the Scandinavian Society of Anaesthesiologists, first appeared in 1957. Initially a quarterly journal it, too, soon became bimonthly.

**TABLE**

**Growth of the World's Anesthesia Literature by Decades***

| | 1920 | 1930 | 1940 | 1950 | 1960 | 1970 | 1980 |
|---|---|---|---|---|---|---|---|
| Am J Anesth Analg (1914) | Q | | | | | | |
| Anesth Analg (1922) | | B | B | B | B | B | M |
| Br J Anaesth (1923) | | Q | Q | Q | M | M | M |
| Anesthesiology (1940) | | | B | B | B | M | M |
| Anesth Analg (Paris) (1944) | | | | B | B | B | B |
| Anaesthesia (1946) | | | | Q | Q | Q | B |
| Anaesthesist (1952) | | | | | M | M | M |
| Can Anaesth Soc J (1954) | | | | | B | B | B |
| Acta Anaesthesiol Scand (1957) | | | | | B | B | B |
| Total issues per year | 4 | 10 | 16 | 26 | 58 | 64 | 72 |

* Q, quarterly; B, bimonthly; M, monthly.

The continued, almost inexorable growth of the world's anesthesia literature over the 60 years from 1920 (4 issues per year) to 1980 (72 issues per year) can be seen in the Table. This is, however, but the tip of an iceberg. Many other equally important and outstanding anesthesia journals, not included in the Table, have also appeared over the years.* The Table does, nonetheless, reflect the steady increase in the amount of material published by and for anesthesiologists throughout the world. Not only has the number of anesthesia journals increased, but the frequency of publication has also progressively increased. Journals that started off as quarterly publications invariably found it necessary to go to monthly or bimonthly publication. With almost equal regularity those that published bimonthly have progressed to monthly publication. That ANESTHESIA AND ANALGESIA now goes to monthly publication is yet another manifestation of the fact that the number of people in anesthesia throughout the world, the breadth of their interests, and the complexity of anesthesiology continue to increase at such a pace that what sufficed as adequate outlets for publication of material relating to anesthesia in the past is no longer sufficient. As the specialty has grown, so, too, has its publications.

The health, vigor, and scientific basis of any discipline can be judged by the quality and quantity of its literature. The growth of the anesthesia literature over the years tells us that anesthesia is globally doing well indeed. We can be proud of this record.

Nicholas M. Greene, MD
*Editor in Chief*

---

* Inclusio unius non exclusio alterius. Space simply does not permit inclusion of all the meritorious anesthesia journals presently published.

ANESTH ANALG
59:3-10, 1980

# A Computer-Assisted Preanesthesia Interview: Value of a Computer-Generated Summary of Patient's Historical Information in the Preanesthesia Visit

**Bonnie Marshall Tompkins, MD,* Willis J. Tompkins, PhD,† Elissa Loder, BA,‡ and Anne F. Noonan, MS§**

---

TOMPKINS, B. M., TOMPKINS, W. J., LODER, E., AND NOONAN, A. F.: A computer-assisted preanesthesia interview: value of a computer-generated summary of patient's historical information in the preanesthesia visit. Anesth Analg 59:3–10, 1980.

A computer-assisted preanesthesia historical interview and a computer-generated summary have been developed as an aid for preanesthesia rounds. Using a video monitor and a keyboard computer terminal, patients were questioned regarding previous medical, surgical, and anesthetic history, medications, allergies, and other items of particular interest to the anesthesiologist. Computer-generated data were compared to those derived from personal interviewing of patients by anesthesiologists.

The computer interview was more accurate (96%, $p < 0.0005$) and less variable than the anesthesiologists in listing correct positive and negative historical information. When the computer interview summary was used in the preanesthesia visit (study 2) the anesthesiologists' assimilation of historical information was greater (82.18%, $p < 0.005$) than when the summary was not used during the preanesthesia visit (73.75%) (study 1). When only positive symptoms and conditions were compared, however, the difference between the computer and the anesthesiologists became more obvious, with more positive findings listed by the computer than by the anesthesiologists. Items missed by anesthesiologists included angina, myocardial infarction, recent upper respiratory infection, asthma, and low back pain.

There was stronger agreement between the computer summary and the anesthesiologists in study 2 than in study 1. Items showing improved agreement ($p < 0.05$) from study 1 to 2 were a history of having had a local anesthetic, including adverse reactions, level of physical activity, alcohol use, and smoking. The computer was more correct ($p < 0.05$) than the anesthesiologists in more items in study 1 than in study 2.

These findings suggest that a computer-generated summary of the preanesthesia history can enhance the anesthesiologists' assimilation of pertinent information. The computer interview was seen by the physicians as an effective aid, and it was accepted well by patients.

**Key Words:** COMPUTERS: anesthesia interviews; RECORDS, Anesthesia: preoperative.

---

* Assistant Professor, Department of Anesthesiology, University of Wisconsin Center for Health Sciences.

† Assistant Professor, Department of Electrical and Computer Engineering, University of Wisconsin.

‡ Specialist, Department of Medicine, University of Wisconsin Center for Health Sciences.

§ Project Assistant, Department of Computer Science, University of Wisconsin.

Received from the Department of Anesthesiology, University of Wisconsin Center for Health Sciences, B6/381 Clinical Science Center, 600 Highland Avenue, Madison, Wisconsin 53792. Accepted for publication August 7, 1979.

Reprint requests to Dr. Tompkins.

LOGISTICAL aspects of the surgical schedule and preoperative anesthesia rounds may often preclude thorough questioning of the patient on important historical items. Efficient and accurate transfer of this historical information from one member of the anesthesia care team to another is often impossible. The anesthetist needs an accessible, readable summary of historical information that he or she would ideally elicit from the patient if time and circumstance allowed.

Computers have been programmed successfully to take a medical history directly from the patient.[1] Questionnaires designed to gather information on allergic,[1-3] gynecologic,[4] psychiatric,[5, 6] venereal disease,[7] drug abuse,[8] and emergency room histories[9] have been implemented as well. Other workers[10-13] have implemented a detailed computer-automated preanesthetic questionnaire which is part of a complex clinical decision-making system for anesthesia.

Investigators have shown that patient-machine rapport is quickly and easily established[3] and that users react quite positively to the experience of dealing with the computer.[3, 14] Computers record information more completely and more accurately than physicians.[7, 9, 14] Patients may prefer the computer over the physician as the history taker,[3] and at times patients are more honest in a computer interview than in a verbal interview with respect to topics such as drug abuse,[8] emotional problems,[15] or smoking history.[16]

A computer-assisted preanesthesia interview has been designed for rapid, reliable collection and convenient display of preanesthetic patient historical information. Studies presented here were designed to compare the computer-generated historical summary with the anesthesiologist's historical information, and to determine whether use of this summary in the preoperative visit improves the physician's assimilation of patient historical information.

## Methods and Materials

Institutional approval for these studies and written informed consent were obtained. The initial computerized patient interview was incorporated into the admissions procedure and took approximately 45 minutes for the patient to complete. Information was directly entered by the patient and stored in the computer for immediate retrieval and further study.

Although an interviewer aide supervised the initial uptake of demographic and medical information and was available throughout for questions or problems, a short instructional program was included in the computer interview which allowed the patient to complete the interview without immediate supervision. A set of teaching frames informed the patient about different types of anesthesia. A concise two-page summary was generated on a line-printer, checked by the patient for errors, and a copy of the summary was given to the patient for his or her own records. The patient's privacy was assured by limiting access to the computer to those who were cognizant of a secret password.

### Logic Design and Interview Construction

The interview, for use on a Digital Equipment Corporation PDP-15 computer, was written with the Beth Israel Converse Interviewing System, a Meditech Information Interchange System (MIIS) language program which facilitates the creation, editing, and operation of an interactive interview containing complex branching logic.[17] This system used a direct computer-patient interviewing process with immediate storage of information. A video monitor was connected to the computer by an acoustic coupler and telephone. Questions were presented in frames with sequences of choices on the video monitor and the patient answered by pressing keys on a typewriter-like device or computer terminal keyboard. Within 10 minutes of completion of the interview the stored responses were converted to summary information and printed out.

For each frame or question and possible answer choices, the content and branching logic was defined. Branching logic for a particular frame was specified in terms of the patient's response to that frame and/or the previous frame. Responses to frames were either open text in the patient's own words, or multiple choice responses.

For both types of questions, open text or multiple choice, the predetermined branching pattern known as response logic was entered at the time of frame construction. Latency logic was also entered and determined the length of time the question appeared on the screen. After a specified time the frame automatically skipped to a fixed frame that reminded the respondent that he had not yet answered the question. A question had to be answered before the frame would branch to the next question. The final frame assigned a permanent storage number to the patient and advanced automatically to the transfer of responses into summarized form. The computer summary information sequence was written with the Summary Construction Program of the Converse system.[17] To list information in the summary, a text phrase in medical terminology was defined along with the conditions under which that phrase was to be printed in the summary. The interview consisted initially of a branching logic scheme of 243 frames and was edited down to 208 frames.

The body of the preanesthesia interview was made up of questions similar to those asked by the anesthesiologists during the preoperative visit including the surgical and anesthetic history, a pertinent system review, dental information, social history, family anesthetic history, medications and allergies, and questions about the patient's current level of anxiety. Ten anxiety symptoms taken from the Hopkins Symptoms Check List,[6] a computerized psychiatric interview, were included to assess the patient's current level of anxiety.

### Study Design

Two separate studies were done to evaluate the effectiveness of a computer-generated preanesthetic historical summary. In study 1 the computer-generated summary was withheld from the anesthesiologist until the study process had been completed. In study 2 the computer summary was given to the anesthesiologist for use during the preoperative visit. After giving written informed consent 84 patients admitted for surgery, i.e., 42 patients in each study, were interviewed by computer. To assess the eventual assimilation or working knowledge of historical information, the anesthesiologists were questioned during or immediately following surgery on the same historical items or categories that were included in the computer summary.

The anesthesiologists' information and the computer summary information were compared for agreement or disagreement, for correct and incorrect answers, and for positive symptoms elicited by each. In instances where the computer and anesthesiologist agreed, both were assumed to be correct; where there was disagreement, a correct answer was defined differently depending on the item. For certain items that were difficult to document, the computer summary, that is the patient's answer, was considered correct. These items included level of physical activity, smoking, and alcohol intake. For the most recent and past surgical history, when disagreement occurred the medical record was consulted and defined as correct. For most other items, a positive symptom or finding listed by either the computer summary or the physician was considered correct. These items included family history of anesthesia, history of having had a local anesthetic including symptoms of side effects or allergy, the system review, pertinent dental information, current medications, and allergies.

Of 33 participating anesthesiologists 28 were requested to weight subjectively on a numerical rating of 1 to 10 the importance of asking each historical question under ideal circumstances. All items with the exception of hometown and occupation were strongly recommended (Table 1). Each item, when correct was multiplied by its mean relative value rounded off to the nearest whole number. Hence, when all items were summed for each patient, the subjective relative importance of each item was to some degree reflected in the total patient score, or the relative value score.

Only informational categories appearing in the computer summary were evaluated. For each historical item the percent correct was computed for the computer and for the anesthesiologist. Each of the 42 patient relative value scores attained by the computer and by the anesthesiologist was converted to an achievement score by dividing the attained score by the maximum possible relative value points.

Within each study a single sample chi-square test was used to show on which items the computer and anesthesiologists agreed, and were therefore both correct. When disagreement occurred a sign test showed on which items the computer was more correct than the anesthesiologists. A 2 x 2 chi-square test was used to determine on which items there was improved agreement between studies 1 and 2.

A single-tailed *t*-test for paired observations was used to compare within each study the relative value scores attained by the computer and by the anesthesiologist in each of 42 patients. A single-tailed *t*-test for unpaired observations was used to test whether the anesthesiologists' achievement scores improved between studies. Within each study, 27 historical items in study 1 were compared and 34 in study 2. The original 27 items were compared between study 1 and study 2.

## Results

The computer-generated summary is a composite of important historical items presented in subsections similar to a typical patient history (Fig 1). It is a short, easily read form.

### Evaluation by Patient Relative Value Score

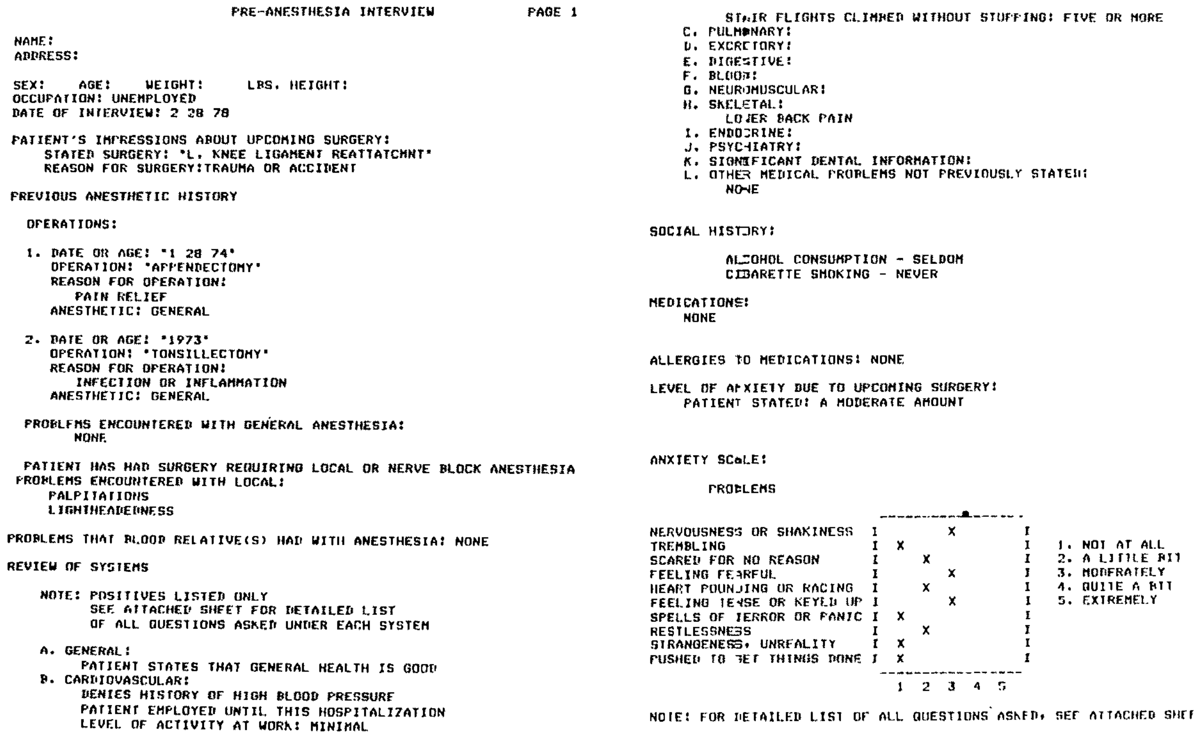
It was anticipated that the anesthesiologist's subjec-

**TABLE 1**
**X̄ Relative Value For 34 Historical Items**

| | Not important | Minimally recommended | | Moderately recommended | | Strongly recommended | | Very strongly recommended | | Essential |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Hometown | | | x | | | | | | | |
| Occupation | | | | | | x | | | | |
| Most recent surgery | | | | | | | | | | |
| Date | | | | | | | | | x | |
| Name | | | | | | | | x | | |
| Anesthetic | | | | | | | | | x | |
| Problems | | | | | | | | | x | |
| Past surgery | | | | | | | | | | |
| Date | | | | | | | x | | | |
| Name | | | | | | | | x | | |
| Anesthetic | | | | | | | | x | | |
| Problems | | | | | | | | | x | |
| Local anesthesia history | | | | | | | | x | | |
| Problems with local anesthesia | | | | | | | | x | | |
| Family history of problems with anesthesia | | | | | | | | | x | |
| Review of systems | | | | | | | | | | |
| Cardiac | | | | | | | | | | |
| Hypertension | | | | | | | | | | x |
| Congestive heart failure | | | | | | | | | | x |
| Rheumatic fever | | | | | | | | | x | |
| Angina | | | | | | | | | | x |
| Other cardiovascular | | | | | | | | | x | |
| Activity | | | | | | | | x | | |
| Pulmonary | | | | | | | | | x | |
| Recent upper respiratory infection | | | | | | | | | | x |
| Renal/excretory | | | | | | | | | x | |
| Hepatic/digestive | | | | | | | | | x | |
| Endocrine/metabolic | | | | | | | | | x | |
| Skeletal | | | | | | | | | x | |
| CNS/muscular | | | | | | | | | x | |
| Hematologic | | | | | | | | | x | |
| Psychiatric | | | | | | | x | | | |
| Social history | | | | | | | | | | |
| Alcohol | | | | | | | | x | | |
| Tobacco | | | | | | | | x | | |
| Anxiety level | | | | | | | x | | | |
| Current medications | | | | | | | | | x | |
| Allergies | | | | | | | | | | x |
| Dental | | | | | | | | x | | |

tive rating of importance of an item would be reflected in the percent correct A mild but statistically significant correlation was shown between the mean relative value of the historical item and the percent correct by the anesthesiologists ($r = 0.6256$, $p < 0.05$) (study 1). This correlation showed no improvement between studies 1 and 2 ($r = 0.6220$, $p < 0.05$) (study 2). Computation of individual weighted patient scores, however, permitted the use of the more powerful nonparametric statistical tests.

A scattergram of relative value scores shows the difference between the computer summary and the anesthesiologists within each study (Fig 2). With the Sign test the computer score was shown to be higher in 38 of 42 cases in study 1 ($p < 0.001$, $z = 5.25$) and in 40 of 42 cases in study 2 ($p < 0.001$, $z = 5.86$). The mean computer summary relative value score for 42 patients was higher than the anesthesiologists' ($p < 0.0005$) in both studies 1 and 2 (Table 2). In each study the computer scores were less variable than the anesthesiologists' and the anesthesiologists' variance did not improve between study 1 and study 2. The



```
                     PRE-ANESTHESIA INTERVIEW          PAGE 1

NAME:
ADDRESS:

SEX:    AGE:    WEIGHT:     LBS. HEIGHT:
OCCUPATION: UNEMPLOYED
DATE OF INTERVIEW: 2 28 78

PATIENT'S IMPRESSIONS ABOUT UPCOMING SURGERY:
    STATED SURGERY: 'L. KNEE LIGAMENT REATTATCHMNT'
    REASON FOR SURGERY:TRAUMA OR ACCIDENT

PREVIOUS ANESTHETIC HISTORY

  OPERATIONS:

  1. DATE OR AGE: '1 28 74'
     OPERATION: 'APPENDECTOMY'
     REASON FOR OPERATION:
        PAIN RELIEF
     ANESTHETIC: GENERAL

  2. DATE OR AGE: '1973'
     OPERATION: 'TONSILLECTOMY'
     REASON FOR OPERATION:
        INFECTION OR INFLAMMATION
     ANESTHETIC: GENERAL

  PROBLEMS ENCOUNTERED WITH GENERAL ANESTHESIA:
        NONE

  PATIENT HAS HAD SURGERY REQUIRING LOCAL OR NERVE BLOCK ANESTHESIA
 PROBLEMS ENCOUNTERED WITH LOCAL:
    PALPITATIONS
    LIGHTHEADEDNESS

PROBLEMS THAT BLOOD RELATIVE(S) HAD WITH ANESTHESIA: NONE

REVIEW OF SYSTEMS

    NOTE: POSITIVES LISTED ONLY
          SEE ATTACHED SHEET FOR DETAILED LIST
          OF ALL QUESTIONS ASKED UNDER EACH SYSTEM

    A. GENERAL:
         PATIENT STATES THAT GENERAL HEALTH IS GOOD
    B. CARDIOVASCULAR:
         DENIES HISTORY OF HIGH BLOOD PRESSURE
         PATIENT EMPLOYED UNTIL THIS HOSPITALIZATION
         LEVEL OF ACTIVITY AT WORK: MINIMAL
```

```
         STAIR FLIGHTS CLIMBED WITHOUT STUFFING: FIVE OR MORE
    C. PULMONARY:
    D. EXCRETORY:
    E. DIGESTIVE:
    F. BLOOD:
    G. NEUROMUSCULAR:
    H. SKELETAL:
         LOWER BACK PAIN
    I. ENDOCRINE:
    J. PSYCHIATRY:
    K. SIGNIFICANT DENTAL INFORMATION:
    L. OTHER MEDICAL PROBLEMS NOT PREVIOUSLY STATED:
         NONE


SOCIAL HISTORY:

         ALCOHOL CONSUMPTION - SELDOM
         CIGARETTE SMOKING - NEVER

MEDICATIONS:
    NONE


ALLERGIES TO MEDICATIONS: NONE

LEVEL OF ANXIETY DUE TO UPCOMING SURGERY:
    PATIENT STATED: A MODERATE AMOUNT



ANXIETY SCALE:

      PROBLEMS

                               -----------------
NERVOUSNESS OR SHAKINESS   I         X        I
TREMBLING                  I   X              I   1. NOT AT ALL
SCARED FOR NO REASON       I      X           I   2. A LITTLE BIT
FEELING FEARFUL            I         X        I   3. MODERATELY
HEART POUNDING OR RACING   I      X           I   4. QUITE A BIT
FEELING TENSE OR KEYED UP  I         X        I   5. EXTREMELY
SPELLS OF TERROR OR PANIC  I   X              I
RESTLESSNESS               I      X           I
STRANGENESS, UNREALITY     I   X              I
PUSHED TO GET THINGS DONE  I   X              I
                               -----------------
                               1  2  3  4  5

NOTE: FOR DETAILED LIST OF ALL QUESTIONS ASKED, SEE ATTACHED SHEET
```

FIG 1. Computer-generated summary of preanesthesia historical information. A comprehensive list of information asked is attached to the summary when presented to the anesthesiologist.

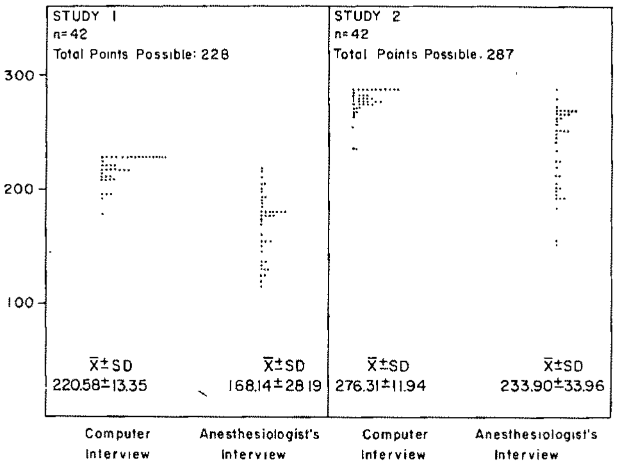


FIG 2. Total relative value scores for each patient attained by the computer summary and by the anesthesiologist. Each correct historical item was multiplied by the relative value of the item. The resulting values were summed to obtain the total relative value score.

anesthesiologists' achievement score in study 2 was greater than in study 1 ( $p < 0.005$) (Table 2).

## Evaluation by Historical Item

Strong agreement ( $p < 0.05$) between the computer summaries and the anesthesiologists' summaries was demonstrated in 70% of items in study 1 and in 87% of items in study 2. Local anesthetic history, level of physical activity, alcohol use, and smoking showed improved agreement in study 2 ( $p < 0.05$).

Between study 1 and study 2, 26 of 27 items evaluated showed a change in the percent correct for the anesthesiologists; 23 items improved, 3 items worsened, and 1 remained the same (Fig 3). The computer summary scores changed little between studies 1 and 2. In nearly all items in both studies the computer had more correct information than the anesthesiologists. The computer was more correct ( $p < 0.05$) than the anesthesiologist in 61% of items in study 1 and only in 39% of items in study 2.

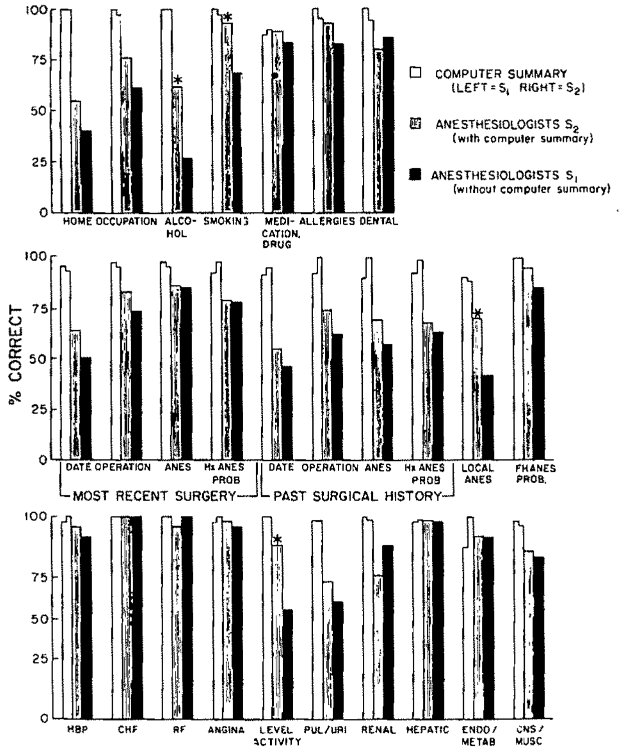
In addition to percent correct, for which credit was given for correct positive and negative findings, the number of positives alone elicited by the computer and the anesthesiologists for items under system review were compared (Table 3). It was evident that for those items showing a high percent correct, with little difference between the anesthesiologists and the computer (Fig 3), there were few positive historical symptoms. These items were high blood pressure (HBP), congestive heart failure (CHF), rheumatic fever (RF), angina, and hepatic and endocrine/metabolic diseases. For items where a greater number of positive

**TABLE 2**

**Relative Value Scores and Overall Achievement Score (%) for 42 Patients in Study 1 (without Summary) and Study 2 (with Summary)**

| | Study 1 (S1) | | Study 2 (S2) | |
|---|---|---|---|---|
| | Computer Summary ($C_1$) | Anesthesiologists ($A_1$) | Computer Summary ($C_2$) | Anesthesiologists ($A_2$) |
| Historical items evaluated | 27 | | 34 | |
| Total possible score | 228 | | 287 | |
| Attained score ($\bar{X} \pm$ SD) | 220.58 ± 13.35 | 168.14 ± 28.19*† | 276.31 ± 11.94 | 233.90 ± 33.96*† |
| Achievement score (%) ($\bar{X} \pm$ SD) | 96.75 ± 5.26 | 73.75 ± 12.52 | 96.40 ± 4.19 | 82.18 ± 12.28‡ |

* $p < 0.0005$, (mean $C_1$ > mean $A_1$, $t = 10.17$; mean $C_2$ > mean $A_2$, $t = 7.32$).
† $p < 0.05$ (variance $C_1$ < variance $A_1$, $F = 5.66$; variance $C_2$ < variance $A_2$, $F = 8.59$).
‡ $p < 0.005$ (mean $A_2$ > mean $A_1$, $t = 3.11$).



*p< 05 (ANES $S_2$ > ANES $S_1$)

FIG 3. Percent of correct answers for historical items on the computer interview. Percent correct for each historical item was obtained by summing correct answers for 42 patients and dividing by total possible correct answers.

symptoms were listed by the patient, a greater discrepancy between the computer and the anesthesiologists was evident. Those items were other cardiovascular symptoms, pulmonary/upper respiratory infection (PUL/URI), and renal and central nervous system/muscular disease (CNS/MUSC). In two of those items, other cardiovascular and pulmonary/upper respiratory infection, there was definite improvement in the anesthesiologists' performance between studies 1 and 2, suggesting that the computer interview summary facilitated assimilation of historical information when used in the preoperative visit. For renal history, an increased number of positive findings in study 2 was evident because cystitis was added to the symptom list, an item that anesthesiologists rarely asked about. This accounts for fewer correct answers elicited by the anesthesiologists than by the computer in study 2 than in study 1.

Inspection of positive findings missed by the anesthesiologists showed that items asked by the computer were too numerous and varied to be realistically asked by every anesthesiologist of each patient. Missed positives included a history of high blood pressure, angina, myocardial infarction, pulmonary symptoms, hepatitis, nephritis, and skeletal problems. Positives missed by the computer were fewer but included a history of seizures, poliomyelitis, and thyroid disease. It appears that the anesthesiologists frequently did not question patients on many items but guessed at the answers, correctly guessing negatives but often missing positives. This accounts for the lower percentage of correct positive symptoms but a relatively high percentage of correct negatives.

Participating physicians in study 2 were asked to comment on several aspects of the computer interview. The comments indicate that most physicians found the interview summary helpful and that frequently it prompted them to ask more questions. On occasion summary statements were misleading or incomplete, and in approximately one fourth of the cases the preanesthesia visit time was lengthened. Only two participating physicians were fearful that computer histories might impair patient care.

Misleading information on the computer summary consisted of several symptom descriptions selected by patients which upon further questioning by the anesthesiologist were considered not significant or were attributed to some other condition. These symptoms,

**TABLE 3**

**Positive Historical Symptoms or Conditions Elicited by Computer and Anesthesiologists**

| | Hypertension | Rheumatic fever | Congestive heart failure | Angina | Other cardiovascular | Pulmonary/ upper respiratory infection | Renal | Hepatic | Endocrine/ Metabolic | CNS/ Muscular |
|---|---|---|---|---|---|---|---|---|---|---|
| Study 1 | | | | | | | | | | |
| Positive symptoms | 4 | 1 | 0 | 3 | 15 | 26 | 5 | 4 | 6 | 11 |
| Positive by computer | 4 | 1 | | 3 | 14 | 24 | 5 | 4 | 5 | 10 |
| % | 100 | 100 | | 100 | 93 | 92 | 100 | 100 | 83 | 91 |
| Positive by anesthesiologists | 3 | 1 | | 2 | 3 | 10 | 2 | 3 | 4 | 3 |
| % | 75 | 100 | | 67 | 20 | 38 | 40 | 75 | 67 | 27 |
| Study 2 | | | | | | | | | | |
| Positive symptoms | 4 | 1 | 0 | 1 | 37 | 43 | 16 | 1 | 6 | 8 |
| Positive by computer | 4 | 1 | | 1 | 35 | 40 | 16 | 0 | 6 | 6 |
| % | 100 | 100 | | 100 | 95 | 93 | 100 | 0 | 100 | 75 |
| Positive by anesthesiologists | 3 | 0 | | 0 | 17 | 21 | 4 | 1 | 4 | 4 |
| % | 75 | 0 | | 0 | 46 | 49 | 25 | 100 | 67 | 50 |

which may be interpreted as interview summary false-positives, were angina (listed twice) and temperature rise with anesthesia, muscle paralysis, and kidney failure (each listed once).

When studies 1 and 2 were combined there were 93 corrections made by 50 patients on their respective computer interview summaries, confirming that patients did make errors and that it was necessary for them to edit and correct their interview summary before it was presented to the physician or placed on the chart.

Patients' impressions about the computer interview were generally favorable. Of 84 patients 62 commented; 66% of the comments were favorable, 24% neutral, and 10% unfavorable.

## Discussion

These studies demonstrate that the computer-assisted preanesthesia interview is more accurate and less variable than the anesthesiologists' preanesthesia interview in gathering preoperative historical information. The data also indicate that the anesthesiologists' assimilation of patient historical information improved when the computer summary was used during the preoperative visit.

Although the computer summary improves the anesthesiologists' awareness of historical information, it still does not bring the achievement score of the anesthesiologists up to that of the computer summary. Human factors of motivation, recall, fatigue, and pressure to save time are not eliminated by computer aids. Error or elimination due to information overload, however, may be corrected by use of computer reminders.[18]

In some items in the present study, such as cardiovascular and hepatic history, the anesthesiologists performed consistently well, with or without the computer summary. In these studies, however, few patients in fact had symptoms of cardiac disease and the physician could get the correct answer without actually having asked the patient. In the patient for whom symptom reviews were positive, the computer elicited the positives more often than did the anesthesiologists.

Other factors may have caused some differences between study 1 and 2. The ongoing development of the interview was in progress and wording changes in several computer questions were made. These would have influenced only the computer scores, which did not differ significantly between study 1 and 2.

Since these studies were done sequentially, and since anesthesiologists who participated in study 1 also participated in study 2, a training effect may have occurred. Some anesthetists may have learned to ask certain questions that they did not usually ask in the preoperative visit prior to the study. The training effect may be the mechanism by which the computer summary increased the anesthesiologists' assimilation of preoperative historical information in this study. If such were true, it would suggest that a computer interview is in fact not redundant but rather that it improves care by eventually strengthening physicians' history taking habits. This study does not prove or disprove a training effect. However, in a study[19] of computer suggestions for patient management, a crossover design ruled out a training effect.

Are computer history aids in medical care cost-effective? Are quality of patient care and/or the physician's sense of preparedness improved by computer history interviews? These questions are at present unanswered. Because the course and conduct of anesthesia seldom markedly alters the patient's eventual outcome except in the seriously ill, it is difficult to determine whether a certain treatment, method, practice, or medical aid improves patient care. Several studies suggest however that computerized patient information systems do in fact improve care. Physician responses to clinical signs, symptoms, or diagnostic tests are increased by computer suggestions about the management of clinical events.[18] In a randomized controlled trial of computer-held medical records in hypertensive patients certain symptoms and risk factors were recognized more often when the computer system was used.[19] In another study,[11] using a Clinical Decision Support System for anesthesia, complications were correctly anticipated in four of five patients. The computer interview described in the present studies allowed the anesthesiologist to focus on previously extracted important findings in the patient history. On a number of occasions further questioning was prompted by statements on the interview summary.

In many clinical settings the preanesthesia visit is of necessity cursory. Many anesthesiologists have felt the stress of anesthetizing an unfamiliar patient at the last minute. The computer summary, if available on a routine basis, might reduce this work-related anxiety and minimize the pressure to complete rounds, allowing for a more effective preoperative visit. In addition, it would enhance assimilation of important historical information. Patient comments in these studies suggest that the computer interview might generate and reinforce optimistic feelings about the perioperative experience. Computer technology is advancing rapidly and has invaded the practice of medicine. Computers are one of the few items with a rapidly declining price, and with increased use the cost per patient is diminishing. The computer-assisted medical interview becomes cost-effective when employed on a computer committed to additional projects.

A computer-assisted preanesthesia interview and summary has been developed as an adjunct to the preanesthesia visit. The computer interview is more accurate than the anesthesiologists in eliciting historical information and, when used during the preanesthesia visit, it improves the anesthesiologists' retention of pertinent historical information.

## ACKNOWLEDGMENTS

The authors thank Marjorie H. Klein, PhD, for statistical consultation, Lawrence J. Van Cura, MS, John H. Greist, MD, Susan R. Frey, BS, and Sandra M. Bass, MA for suggestions.

## REFERENCES

1. Slack WV, Hicks GP, Reed CE, et al: A computer-based medical-history system. N Engl J Med 274:194–198, 1966
2. Pantin CFA, Merrett J, Leighton M, et al: Computer analysis of allergic histories taken by questionnaire. Clin Allergy 8:227–233, 1978
3. Slack WV, Van Cura LJ: Patient reaction to computer-based medical interviewing. Comput Biomed Res 1:527–531, 1968
4. Peckham BM, Slack WV, Carr WF, et al: Computerized data collection in the management of uterine cancer. Clin Obstet Gynecol 10:1003–1015, 1967
5. Griest JH, Gustafson DH, Stauss FF, et al: A computer interview for suicide-risk prevention. Am J Psychiatry 130:1327–1332, 1973
6. Griest JH, Klein MH, Van Cura LJ: A computer interview for psychiatric patient target symptoms. Arch Gen Psychiatry 29: 247–253, 1973
7. Van Cura LJ, Jensen N, Griest JH, et al: Venereal disease: interviewing and teaching by computer. Am J Public Health 65:1159–1164, 1975
8. Griest JH, Klein MH, Van Cura LJ, et al: The computer interview as a medium for collecting questionnaire data on drug use; predicting adolescent drug use, in Predicting Adolescent Drug Use: A Review of Issues, Methods and Correlates. Edited by DJ Lettieri. Washington, DC, Government Printing Office, 1975, pp 147–164
9. Griest JH, Van Cura LJ, Kneppreth NP: A computer interview for emergency room patients. Comput Biomed Res 6:257–265, 1973
10. Chodoff P, Helrich M: Construction of an automated system for the collection and processing of preoperative data. Anesth Analg 48:870–876, 1969
11. Chodoff P, Gianaris C: A nurse-computer assisted preoperative anesthesia management system. Comput Biomed Res 6:371–392, 1973
12. Chodoff P, Drews JH: Decision making in anesthesiology: experiences with a new automated technique for interviewing. JAMA 218:85–88, 1971
13. Wellner C, Bauman WA, Chodoff P, et al: A computer system to aid clinical decisions. South Med Bull 57:49–52, 1969
14. Grossman JH, Octo Barnett G, Mcguire MT, et al: Evaluation of computer-acquired patient histories. JAMA 215:1286–1291, 1971
15. Slack WV, Slack CW: Patient-computer dialogue. N Engl J Med 286:1304–1309, 1972
16. Anonymous: Special feature: medical case histories by computer. Biomed Eng 11:353–354, 1976
17. Van Cura LJ, Slack WV, Frey SR: Elements of a computer medical interview system. Biomed Sci Instrum 8:33–42, 1971
18. McDonald CJ: Protocol-based computer reminders, the quality of care and the non-perfectability of man. N Engl J Med 295: 1351–1355, 1976
19. Bulpitt CJ, Beilin LJ, Coles EC, et al: Randomized controlled trial of computer-held medical records in hypertensive patients. Br Med J 1:677–679, 1976

ANESTH ANALG
59:11-18, 1980

# Peripheral Vascular and Direct Cardiac Effects of Digoxin in the Calf

**Theodore H. Stanley, MD,* Judd K. Lunn, MD,† Wen-Shin Liu, MD,† Scott Gentry, BS,‡ and Don Olsen, DVM§**

---

STANLEY, T. H., LUNN, J. K., LIU, W.-S., GENTRY, S., AND OLSEN, D.: Peripheral vascular and direct cardiac effects of digoxin in the calf. Anesth Analg 59:11–18, 1980.

Peripheral vascular and direct cardiac effects of intravenous digoxin (5, 10, and 15 μg/kg) were determined in a pharmacologic animal model, the unanesthetized calf before and after replacement of its natural heart (NH) with a pneumatically driven artificial heart (AH). All doses of digoxin significantly increased cardiac output and stroke volume 30 and 60 minutes after administration before and after AH replacement. Increases in output and stroke volume were greater before AH replacement than after. Increases in output were similar with all doses of digoxin in AH calves but greater with increasing doses in NH calves. Digoxin produced significant and similar increases in systemic vascular resistance within 5 minutes and significant and similar decreases 25 and 55 minutes later in NH and AH calves. While increases in systemic vascular resistance were greater with 10 and 15 μg/kg than with 5 μg/kg of digoxin, decreases in resistance were similar at all doses of digoxin in NH and AH animals. Mean aortic blood pressure transiently increased 5 minutes after all doses of digoxin in NH calves. Heart rate was reduced by all doses of digoxin 5 minutes after administration in NH calves but was unchanged from control in subsequent measurements. Heart rate was fixed in calves with an AH. Mean right atrial pressure was increased similarly by all doses of digoxin in NH and AH calves 30 and 60 minutes following administration. These data indicate that digoxin had significant peripheral vascular (arterial and venous) effects in the healthy calf and suggest that elevations in cardiac output and stroke volume after its use are partially due to both increases in pre-load and to decreases in systemic vascular resistance (after-load).

**Key Words:** HEART, digoxin.

---

THE ABILITY of digoxin and other cardiac glycosides to increase myocardial contractility is well known.[1-3] A number of reports suggest that these compounds also possess significant peripheral vascular action.[1, 2, 4-6] However, the importance of these latter effects on the total hemodynamic response is not clear. Recent advances in the development of an artificial heart (AH) to replace the natural heart of the patient with uncorrectable or untreatable heart disease have made available a unique animal model for study of the differential cardiovascular effects of drugs with peripheral vascular and direct cardiac inotropic actions.[7-9] This model, the unanesthetized calf before and after its natural heart (NH) is removed and replaced with a pneumatically powered pulsatile AH, not only enables quantitation but also separation of the myocardial effects of a drug from its actions on the peripheral vasculature.[10-11] In the present study,

---

* Professor of Anesthesiology/Surgery.

† Assistant Professor of Anesthesiology.

‡ Research Technician.

§ Associate Research Professor of Surgery.

Received from the Department of Anesthesiology and Division of Artificial Organs, Department of Surgery, The University of Utah College of Medicine, Salt Lake City, Utah 84132. Accepted for publication August 10, 1979.

Supported in part by Contract 69-2181 and Grant HL 13738, National Heart Institute, National Institutes of Health, and the Lad L. and Mary Herick Fund, and Mr. Maurice Warshaw.

Reprint requests to Dr. Stanley at Department of Anesthesiology, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, UT 84132.

the bovine AH model was used to differentiate cardiac and systemic vascular actions following administration of 5, 10, or 15 μg/kg of intravenous digoxin.

## Method

The experimental subjects were 40, 90- to 104-kg, bull calves. Each calf was anesthetized with sodium methohexital, 3 to 5 mg/kg, intravenously, the trachea intubated and anesthesia maintained with halothane, 1 to 2%. A 10-gauge needle was placed percutaneously into the right external jugular vein. With continuous pressure recording, a 7 Fr Swan-Ganz triple-lumen catheter was threaded through the needle, the right ventricle, and into the proximal pulmonary artery. Another catheter (14 Fr) was placed percutaneously into the opposite jugular vein and threaded into the right atrium. A third catheter (17 Fr) was threaded into the central aorta through the left femoral artery via a small groin incision. Catheter positions were evaluated by fluoroscopy and catheter patency maintained with a dilute heparinized (2 units/ml) solution of Ringer's lactate administered at a rate of 1 to 2 ml/hr via a constant infusion pump. Anesthesia was then terminated and the animals extubated and allowed to recover for 24 to 48 hours.

### Pre-Artificial Heart Implantation Study Procedures

Studies before AH implantation were performed with the calves standing in a metal cage. Arterial blood samples were drawn for blood gas analysis and pH. Following this, the animals breathed 100% oxygen through a specially designed air-tight calf face mask. Collins 3-cm i.d. inspiratory and expiratory "J" valves (model P-304) were attached to the mask portals and the inspiratory valve was connected to a source of oxygen. Pulmonary arterial and aortic blood samples were obtained in duplicate (for oxygen content analysis) after 20 minutes of oxygen breathing, and heart rate and mean pulmonary artery, aortic and right atrial pressures recorded. Oxygen uptake was measured over a 3-minute period within 2 minutes of collection of aortic and pulmonary artery blood samples by removing both "J" valves from the mask portals, attaching one of the portals to a standard 9-L oxygen-filled Collins closed-circuit spirometer equipped with water and $CO_2$ absorbers, and plugging the other portal of the face mask.

Cardiac output was measured by using the Fick equation. Stroke volume was obtained by dividing cardiac output by heart rate.

Blood carbon dioxide tension was measured with a Severinghaus electrode, pH with a Radiometer glass electrode and oxygen tension with a modified Clark electrode. All electrodes were maintained at 39 C (normal for a calf) and frequently recalibrated with standard solutions and gases of known concentration and tension. Temperature corrections were made when necessary using standard bovine blood-gas correction factors. Oxygen saturation was determined using an American Optical Co oximeter and hemoglobin with a Fisher Hemophotometer. Rectal temperature was monitored with a Yellow Springs temperature probe and recording module. It was assumed that 1 g of fully oxygenated calf blood combined with 1.39 ml of oxygen. Blood oxygen content in milliliters per 100 milliliters was calculated from hemoglobin (Hb) capacity, oxygen saturation, and dissolved oxygen according to the following equation:

$$\text{Oxygen content} = (1.39\ \text{g Hb/100 ml blood})\ (\%\ \text{Hb saturation}) + 0.0031 \times \text{Pa}_{O_2}$$

Systemic vascular resistance in dynes/sec/$cm^{-5}$ was calculated from the equation:

$$\text{Systemic vascular resistance} = \frac{\text{Mean aortic pressure (torr)} - \text{mean right atrial pressure (torr)}}{\text{cardiac output (L/min)}} \times 80$$

Following control measurements and with the calves breathing into the spirometer, 5, 10, or 15 μg/kg of digoxin was rapidly given intravenously and after 5, 10, 15, 30, and 60 minutes pulmonary arterial and aortic blood samples were collected; oxygen uptake, heart rate, and pulmonary artery, aortic and right atrial blood pressures were remeasured; and cardiac output was recalculated. Two to 6 days later each calf had its NH replaced with a pneumatically driven AH.

A silicone rubber or polyurethane four-chambered elliptical type of AH was used in these investigations. This type of AH as well as the implantation procedure and the pneumatic driving system employed to pump the heart have been described previously.[9-11]

### Post-Artificial Heart Implantation Study Procedures

Post-AH-implantation studies were initiated 14 to 41 days after the operation when tidal volume was greater than 400 ml, arterial carbon dioxide tension ($\text{Pa}_{CO_2}$) was less than 40 torr, and arterial oxygen tension ($\text{Pa}_{O_2}$) was greater than 70 torr for six or more hours while breathing room air. Additional criteria for acceptance in the study included mean pulmonary artery, aortic and right atrial pressures within 20% of

**TABLE 1**
**Cardiac Output after Digoxin***

| Dosage | Heart | Control | Minutes after digoxin† | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 |
| *µg/kg* | | | | | *liters/min* | | |
| 5 | NH | $8.0 \pm 0.6$ | $7.5 \pm 0.7$ | $8.1 \pm 0.7$ | $8.4 \pm 0.6$ | $9.1 \pm 0.5^{a,d}$ | $9.2 \pm 0.5^{a,d}$ |
| | AH | $7.7 \pm 0.5$ | $7.5 \pm 0.5$ | $7.9 \pm 0.6$ | $7.9 \pm 0.5$ | $8.3 \pm 0.4^{a}$ | $8.4 \pm 0.5^{a}$ |
| 10 | NH | $7.9 \pm 0.5$ | $7.1 \pm 0.6^{a}$ | $7.7 \pm 0.6$ | $8.5 \pm 0.5$ | $9.3 \pm 0.6^{b,d}$ | $9.5 \pm 0.5^{b,d}$ |
| | AH | $7.6 \pm 0.4$ | $6.8 \pm 0.5$ | $7.5 \pm 0.6$ | $7.9 \pm 0.6$ | $8.5 \pm 0.5^{a}$ | $8.5 \pm 0.4^{a}$ |
| 15 | NH | $7.7 \pm 0.6$ | $7.0 \pm 0.5^{a}$ | $7.6 \pm 0.6$ | $8.4 \pm 0.4$ | $9.5 \pm 0.6^{b,d}$ | $9.7 \pm 0.4^{c,e}$ |
| | AH | $7.6 \pm 0.5$ | $7.0 \pm 0.5^{a}$ | $7.6 \pm 0.5$ | $7.8 \pm 0.5$ | $8.5 \pm 0.5^{a}$ | $8.4 \pm 0.5^{a}$ |

* Values are means ± standard deviation. These data represent the mean of a single measurement in each of 20 calves given 5 µg/kg of digoxin and a single measurement in each of 20 additional calves given 10 µg/kg and at another time 15 µg/kg of digoxin. Abbreviations used: NH, normal heart; AH, artificial heart.

† *a*, $p < 0.05$; *b*, $p < 0.025$; *c*, $p < 0.01$: Student's paired *t*-test when compared to controls at the same dosage level; *d*, $p < 0.05$; *e*, $p < 0.025$: Student's paired *t*-test when compared to AH values in the same animal and at the same dosage of digoxin.

pre-AH levels when AH output was adjusted (via heart rate changes) to approximate pre-implantation values. When these criteria were met, arterial blood samples were drawn in duplicate for blood gas and pH analysis; each calf breathed 100% oxygen through the calf face mask; and pre-AH implantation study procedures were repeated.

Mean left atrial pressure was an additional variable available for measurement after AH implantation. Left atrial pressure was obtained, as were right atrial, pulmonary arterial, and aortic pressures and blood samples, from high pressure tubing connected to taps on the artificial atria and vascular grafts attaching the artificial ventricles to the natural pulmonary artery and aorta. Using mean left atrial pressure, it was possible to calculate pulmonary vascular resistance in dynes/sec/cm$^{-5}$ after AH implantation using the following equation:

$$\text{Pulmonary vascular resistance} = \frac{\text{mean pulmonary artery pressure (torr)} - \text{mean left atrial pressure (torr)}}{\text{cardial output (L/min)}} \times 80$$

All data were examined for statistical significance utilizing Student's paired t-test. Data reported represent the mean of a single measurement in each of 20 calves given 5 µg/kg of digoxin before and after AH replacement and in 20 additional calves given 10 µg/kg and at another time‖ 15 µg/kg of digoxin both before and after AH replacement.

## Results

Mean values of arterial pH, $Pa_{CO_2}$, and $Pa_{O_2}$ were within normal limits and similar during control conditions (before administration of all doses of digoxin) prior to and after AH replacement. No dose of digoxin altered $Pa_{CO_2}$ or arterial pH significantly at any time before or after AH replacement.

Mean values of all cardiovascular variables measured were also not significantly different during control conditions before and after AH replacement. Digoxin, 10 and 15 µg/kg, produced significant and similar reductions in cardiac output within 5 minutes in NH and AH calves (Table 1). Digoxin, 5 µg/kg, also reduced cardiac output after 5 minutes in NH and AH calves; these changes were not statistically significant. All doses of digoxin significantly increased cardiac output and stroke volume 30 and 60 minutes after administration before and after AH replacement (Tables 1 and 2). Increases in cardiac output and stroke volume were greater before AH replacement than after. Increases in cardiac output and stroke volume were similar with all doses of digoxin in AH calves but were greater with increasing doses in NH calves.

Digoxin produced significant and similar increases in systemic vascular resistance in 5 minutes and significant and similar decreases 25 and 55 minutes later in NH and AH calves (Table 3). Whereas increases in systemic vascular resistance were greater with higher doses of digoxin, decreases in resistance were similar at all doses of digoxin in both NH and AH animals. Pulmonary vascular resistance was only measured in AH calves and was markedly elevated by all doses of digoxin 5 minutes after administration but unchanged from control values thereafter (Table 3).

Heart rate transiently decreased 5 minutes after all doses of digoxin in NH calves but was unchanged from control values thereafter (Table 4). Heart rate was fixed in AH calves.

---

‖ A minimum of 5 days after administration of the 10 µg/kg dosage when all effects of this dosage would have dissipated.

**TABLE 2**

**Stroke Volume after Digoxin***

| Dosage | Heart | Control | Minutes after digoxin† | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 |
| *μg/kg* | | | *ml* | | | | |
| 5 | NH | 93 ± 10 | 99 ± 13$^{d}$ | 98 ± 10$^{d}$ | 104 ± 9$^{a,d}$ | 107 ± 9$^{b,d}$ | 107 ± 7$^{b,d}$ |
| | AH | 88 ± 8 | 85 ± 12 | 90 ± 9 | 90 ± 8 | 96 ± 8$^{a}$ | 96 ± 6$^{a}$ |
| 10 | NH | 92 ± 9 | 100 ± 13$^{e}$ | 96 ± 10$^{d}$ | 103 ± 12$^{a,d}$ | 110 ± 11$^{b,d}$ | 110 ± 10$^{b,d}$ |
| | AH | 86 ± 11 | 80 ± 9 | 85 ± 10 | 90 ± 9 | 97 ± 10$^{a}$ | 96 ± 9$^{a}$ |
| 15 | NH | 88 ± 10 | 103 ± 12$^{a,e}$ | 94 ± 11 | 104 ± 10$^{b,d}$ | 116 ± 11$^{c,e}$ | 118 ± 10$^{c,e}$ |
| | AH | 86 ± 9 | 80 ± 9 | 86 ± 10 | 89 ± 9 | 96 ± 10$^{a}$ | 96 ± 9$^{a}$ |

* Values are means ± standard deviation. These data represent the mean of a single measurement in each of 20 calves given 5 μg/kg of digoxin and a single measurement in each of 20 additional calves given 10 μg/kg and at another time 15 μg/kg of digoxin. Abbreviations used: NH, normal heart; AH, artificial heart.

† *a*, $p < 0.05$; *b*, $p < 0.025$; *c*, $p < 0.01$: Student's paired *t*-test when compared to controls at the same dosage level; *d*, $p < 0.05$, *e*, $p < 0.025$: Student's paired *t*-test when compared to AH values in the same animal and at the same dosage of digoxin.

**TABLE 3**

**Systemic and Pulmonary Vascular Resistance after Digoxin***

| Dosage | Heart | Control | Minutes after digoxin† | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 |
| *μg/kg* | | | *dynes/sec/cm$^{-5}$* | | | | |
| Systemic | | | | | | | |
| 5 | NH | 949 ± 69 | 1,132 ± 61$^{a}$ | 1,002 ± 47 | 954 ± 54 | 861 ± 43$^{a}$ | 840 ± 49$^{a}$ |
| | AH | 1,015 ± 41 | 1,123 ± 55$^{a}$ | 1,013 ± 58 | 949 ± 50 | 940 ± 63$^{a}$ | 907 ± 62$^{a}$ |
| 10 | NH | 960 ± 57 | 1,240 ± 71$^{b}$ | 1,029 ± 66 | 894 ± 59 | 817 ± 54$^{a}$ | 800 ± 48$^{a}$ |
| | AH | 992 ± 64 | 1,282 ± 78$^{b}$ | 1,045 ± 73 | 962 ± 48 | 856 ± 42$^{a}$ | 828 ± 43$^{a}$ |
| 15 | NH | 987 ± 62 | 1,245 ± 65$^{b}$ | 1,031 ± 51 | 924 ± 49 | 817 ± 50$^{a}$ | 804 ± 63$^{a}$ |
| | AH | 979 ± 64 | 1,234 ± 67$^{b}$ | 1,052 ± 69 | 974 ± 58 | 859 ± 51$^{a}$ | 839 ± 60$^{a}$ |
| Pulmonary | | | | | | | |
| 5 | AH | 147 ± 18 | 203 ± 24$^{b}$ | 151 ± 23 | 146 ± 20 | 131 ± 20 | 119 ± 19 |
| 10 | AH | 147 ± 17 | 200 ± 25$^{b}$ | 169 ± 21 | 152 ± 19 | 125 ± 21 | 139 ± 18 |
| 15 | AH | 137 ± 20 | 206 ± 23$^{b}$ | 153 ± 23 | 132 ± 18 | 132 ± 18 | 134 ± 19 |

* Values are means ± standard deviation. These data represent the mean of a single measurement in each of 20 calves given 5 μg/kg of digoxin and a single measurement in each of 20 additional calves given 10 μg/kg and at another time 15 μg/kg of digoxin. Abbreviations used: NH, normal heart; AH, artificial heart.

† *a*, $p < 0.05$; *b*, $p < .025$: Student's paired *t*-test when compared to controls at the same dosage level.

**TABLE 4**

**Heart Rate after Digoxin***

| Dosage | Heart | Control | Minutes after digoxin† | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 |
| *μg/kg* | | | *beats/min* | | | | |
| 5 | NH | 85 ± 10 | 75 ± 7$^{a,d}$ | 82 ± 9 | 81 ± 9 | 85 ± 8 | 86 ± 10 |
| | AH | 88 | 88 | 88 | 88 | 88 | 88 |
| 10 | NH | 86 ± 9 | 71 ± 8$^{b,e}$ | 80 ± 11 | 83 ± 12 | 84 ± 10 | 86 ± 11 |
| | AH | 88 | 68 ± 9$^{b,e}$ | 88 | 88 | 88 | 88 |
| 15 | NH | 85 ± 9 | 88 | 81 ± 10 | 81 ± 11 | 82 ± 12 | 82 ± 10 |
| | AH | 88 | | 88 | 88 | 88 | 88 |

* Values are means ± standard deviation. These data represent the mean of a single measurement in each of 20 calves given 5 μg/kg of digoxin and a single measurement in each of 20 additional calves given 10 μg/kg and at another time 15 μg/kg of digoxin. Abbreviations used: NH, normal heart; AH, artificial heart.

† *a*, $p < 0.05$; *b*, $p < 0.025$: Student's paired *t*-test when compared to controls at the same dosage level; *d*, $p < 0.05$; *e*, $p < 0.025$: Student's paired *t*-test when compared to AH values in the same animal and at the same dosage of digoxin.

Mean pulmonary arterial blood pressure was significantly and similarly increased by all doses of digoxin within 5 minutes in NH and AH calves but returned to control values in all subsequent measurements (Table 5). Mean aortic blood pressures increased 5 minutes after all doses of digoxin in NH calves and after 10 and 15 μg/kg in AH calves (Table 5). Aortic pressures returned to values that were similar to those of control calves after 5 minutes. Mean left atrial pressure was only measured in AH calves and was transiently increased 5 minutes after all doses of digoxin (Table 6). Mean right atrial pressure was not altered by any dose of digoxin in either group of animals until 30 and 60 minutes following administration when right atrial pressure increased slightly but similarly following all doses of digoxin in both groups (Table 6).

## Discussion

The healthy, standing, unanesthetized calf before and after replacement of its natural heart with a

**TABLE 5**
**Mean Aortic and Pulmonary Artery Blood Pressure after Digoxin***

| Dosage | Heart | Control | Minutes after digoxin† | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 |
| *μg/kg* | | | | *torr* | | | |
| Aortic | | | | | | | |
| 5 | NH | 99 ± 9 | 111 ± 10$^a$ | 105 ± 8 | 103 ± 7 | 102 ± 8 | 102 ± 9 |
| | AH | 102 ± 8 | 109 ± 11 | 109 ± 9 | 107 ± 5 | 101 ± 8 | 101 ± 9 |
| 10 | NH | 98 ± 9 | 114 ± 12$^b$ | 104 ± 11 | 100 ± 9 | 102 ± 8 | 103 ± 10 |
| | AH | 98 ± 8 | 113 ± 13$^b$ | 102 ± 13 | 100 ± 9 | 97 ± 9 | 96 ± 9 |
| 15 | NH | 99 ± 10 | 113 ± 13$^b$ | 103 ± 10 | 103 ± 10 | 104 ± 11 | 104 ± 10 |
| | AH | 98 ± 9 | 113 ± 11$^b$ | 105 ± 11 | 100 ± 9 | 99 ± 8 | 99 ± 9 |
| Pulmonary artery | | | | | | | |
| 5 | NH | 19 ± 2 | 27 ± 3$^b$ | 21 ± 3 | 21 ± 3 | 21 ± 4 | 20 ± 4 |
| | AH | 19 ± 3 | 26 ± 2$^b$ | 21 ± 2 | 20 ± 2 | 20 ± 3 | 20 ± 3 |
| 10 | NH | 19 ± 2 | 29 ± 3$^b$ | 22 ± 4 | 20 ± 2 | 20 ± 2 | 20 ± 2 |
| | AH | 19 ± 2 | 27 ± 2$^b$ | 23 ± 3 | 20 ± 3 | 19 ± 2 | 19 ± 2 |
| 15 | NH | 18 ± 2 | 30 ± 3$^b$ | 21 ± 3 | 20 ± 2 | 19 ± 2 | 19 ± 3 |
| | AH | 19 ± 2 | 29 ± 3$^b$ | 23 ± 3 | 19 ± 2 | 19 ± 2 | 19 ± 2 |

* Values are means ± standard deviation. These data represent the mean of a single measurement in each of 20 calves given 5 μg/kg of digoxin and a single measurement in each of 20 additional calves given 10 μg/kg and at another time 15 μg/kg of digoxin. Abbreviations used: NH, normal heart; AH, artificial heart.

† *a*, $p < 0.05$; *b*, $p < 0.025$: Student's paired *t*-test when compared to controls at the same dosage level.

**TABLE 6**
**Mean Right and Left Atrial Pressure after Digoxin***

| Dosage | Heart | Control | Minutes after digoxin† | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 |
| *μg/kg* | | | | | | | |
| Right | | | | | | | |
| 5 | NH | 4 ± 1 | 4 ± 1 | 4 ± 1 | 5 ± 1 | 6 ± 1$^a$ | 6 ± 1$^a$ |
| | AH | 4 ± 1 | 4 ± 2 | 5 ± 2 | 5 ± 1 | 6 ± 2$^a$ | 6 ± 1$^a$ |
| 10 | NH | 4 ± 1 | 4 ± 1 | 5 ± 1 | 5 ± 2 | 7 ± 2$^a$ | 8 ± 2$^a$ |
| | AH | 4 ± 1 | 4 ± 1 | 4 ± 1 | 5 ± 1 | 6 ± 2$^a$ | 8 ± 2$^a$ |
| 15 | NH | 4 ± 1 | 5 ± 1 | 5 ± 2 | 5 ± 1 | 7 ± 2$^a$ | 8 ± 2$^a$ |
| | AH | 5 ± 1 | 5 ± 1 | 5 ± 2 | 5 ± 1 | 6 ± 2 | 8 ± 2$^a$ |
| Left | | | | | | | |
| 5 | AH | 5 ± 1 | 8 ± 1$^a$ | 7 ± 2 | 6 ± 2 | 5 ± 1 | 5 ± 1 |
| 10 | AH | 5 ± 1 | 10 ± 2$^b$ | 7 ± 2 | 7 ± 1 | 6 ± 1 | 4 ± 1 |
| 15 | AH | 6 ± 1 | 11 ± 2$^b$ | 8 ± 2 | 6 ± 2 | 5 ± 1 | 5 ± 1 |

* Values are means ± standard deviation. These data represent the mean of a single measurement in each of 20 calves given 5 μg/kg of digoxin and a single measurement in each of 20 additional calves given 10 μg/kg and at another time 15 μg/kg of digoxin. Abbreviations used: NH, normal heart; AH, artificial heart.

† *a*, $p < 0.05$; *b*, $p < 0.025$: Student's paired *t*-test when compared to controls at the same dosage level.

pneumatically driven artificial heart is a useful model for studies of cardiovascularly active pharmacologic compounds. Besides docility and ease of handling and instrumentation, the bovine artificial heart model enables investigation of drug action in animals in the absence of other pharmacologic or physiologic influences, e.g., anesthesia or artificial respiration, which may modify the cardiovascular manifestations of the compound under investigation. In addition, and more important, utilization of an animal before and after artificial heart implantation for drug investigation alows quantitation and separation of the effect of a compound on the peripheral vascular system (after AH replacement) from its effect on the heart plus the peripheral vascular system (before AH replacement).

The findings of this study using the bovine AH model document the production by intravenous digoxin of marked through transient increases in systemic and pulmonary arterial blood pressures and resistances, a slight decrease in cardiac output, and, in NH calves, a decrease in heart rate soon after administration. Left atrial pressure is also transiently increased by digoxin but right atrial pressure remains unchanged, at least initially. The above changes are replaced by significant increases in right atrial pressure and cardiac output and decreases in systemic vascular resistance 30 and 60 minutes after digoxin.

These data confirm previous work indicating that a marked increase in systemic vascular resistance and decrease in heart rate result in the reduction in cardiac output that is often seen after digitalis preparations are administered to mammals with a normal heart.[3, 12] However, our results also suggest that increases in peripheral resistance after digoxin are dose-dependent and transient in the standing calf and are replaced within a short time by decreases in peripheral resistance which are not dependent on dosage. Decreases in systemic vascular resistance were similar in both NH and AH calves 30 and 60 minutes after digoxin. Increases in right atrial pressure were also similar in both groups 30 and 60 minutes after digoxin. These changes coupled with significantly greater elevations in cardiac output in NH animals than in AH animals suggest that increases in cardiac output after digoxin in intact animals in the absence of congestive heart failure are due to a combination of dose-dependent increases in myocardial contractility and dose-independent decreases in after-load and increases in preload.

The positive inotropic effect of cardiac glycosides on failing mammalian cardiac musculature has been amply demonstrated in the isolated myocardial muscle preparation[13] and man.[14] Other work has demonstrated that digitalis preparations also improve myocardial contractility in the nonfailing mammalian heart.[1] Although direct measurements of myocardial inotropy are not possible in the calf before AH replacement with our experimental procedure, an estimation of change in myocardial contractility after administration of pharmacologically active compounds can be made by comparing hemodynamic alterations following drug administration before and after AH replacement.

Stroke volume changes following pharmacologic administration in NH calves are dependent on alterations in heart rate, pre-load, after-load,¶ and the contractile state of the heart. Our AH has a Starling curve with changes in pre-load and after-load similar to those observed in a calf with a normal heart, i.e., it adjusts itself to changes in venous return and peripheral resistance and is not just a constant volume pump. Consequently, AH calves respond to drug administration in fashion similar to NH calves except their heart rate and contractile state are fixed. Therefore, stroke volume changes in AH calves are solely due to changes in venous return and systemic vascular resistance. In the absence of changes in heart rate, subtraction of stroke volume alterations following drug administration after AH replacement from those occurring following drug administration before AH implantation should yield that amount of stroke volume change that occurred due to drug-induced inotropism. In this study digoxin produced similar alterations in right atrial pressure and systemic vascular resistance in NH and AH calves. While digoxin resulted in comparable changes in cardiac output after 5, 10, and 15 minutes in both groups of animals, thereafter cardiac output increased significantly more in NH calves than AH calves. Thirty minutes after 15 μg/kg of digoxin stroke volume was 12% and 32% and cardiac output 11% and 19% above control volumes in AH calves and NH calves, respectively. We believe the difference in stroke volume and cardiac output between NH calves and AH calves represents the positive inotropic effect of digoxin on NH myocardial musculature.

The influence of digitalis on the peripheral vasculature is controversial. One reason for this is that only a few studies, utilizing a limited number of doses of a variety of compounds, have been performed. In addition, the temporal effects of digoxin on the peripheral vasculature have not been carefully considered. Thus, studies in the dog[15-19] and in man[1, 2, 4, 14, 19, 20] have reported increases, decreases, or no change in peripheral arterial resistance, venous return to the right heart, and arterial, central venous, and right atrial pressures.

---

¶ For simplicity's sake, after-load is equated with peripheral arterial resistance in this discussion. Strictly speaking, after-load = ventricular wall tension developed during ejection.

Our data in this study indicate that in the unanesthetized calf not in heart failure, large doses of digoxin (10 and 15 μg/kg) produce greater increases in systemic vascular resistance early after administration than do smaller doses (5 μg/kg). Our data also demonstrate that all doses of digoxin result in similar decreases in systemic resistance and increases in right atrial pressure. The latter changes are, however, not evident until 30 minutes after administration of the digoxin. Considering the importance of both dosage and time of measurement in our data, it appears clear why the peripheral effects of digitalis have been so controversial.

The doses of digoxin used in this study are within the therapeutic range in the calf, comparable to doses of digoxin administered to man and result in similar digoxin blood levels in the calf and in man (T. H. Stanley and D. Olsen, unpublished data). Still, digoxin is not often used in calves or patients not in congestive heart failure. Therefore, it is difficult to speculate whether the data obtained in this study in calves without cardiac failure are applicable in patients in failure. Furthermore, patients in congestive heart failure often have elevated circulating catecholamine blood levels.[21] Data from this laboratory have demonstrated that circulating catecholamine blood levels in calves 2 weeks after AH replacement are within normal range and similar to those measured before operation.[22] This indicates that in spite of cardiac denervation, the AH calves used in this study and the NH calves were under similar, and probably normal, sympathetic autonomic influences. However, it also appears from studies performed in a few animals, that digoxin results in similar cardiovascular responses as observed in this investigation when administered to calves early after AH implantation (when circulating catecholamines are elevated) and in calves in congestive heart failure (T. H. Stanley and J. Lunn, unpublished data).

The results of this study do not demonstrate the mechanisms responsible for the peripheral effects of digoxin. Explanations should include direct effects of digoxin on vascular smooth muscle[23] or changes secondary to alterations in blood catecholamine concentrations.[4] Explanations do not include an additive or preservative in the preparation (because one was not used), nor do they include reflex changes in peripheral resistance secondary to improved myocardial contractility (because contractility was constant in AH calves). Since alterations in pre-load and after-load change myocardial oxygen demand, an understanding of the effects and mechanisms involved in the peripheral vascular actions of digoxin is important and deserves further study.

## ACKNOWLEDGMENT

The authors thank Myron Laver, MD, for advice and suggestions in the preparation of this manuscript.

## REFERENCES

1. Braunwald E, Bloodwill RD, Goldberg LL, et al: Studies on digitalis. IV. Observations in man on the effects of digitalis preparations on the contractility of the non-failing heart and on total vascular resistance. J Clin Invest 40:52–59, 1961
2. Cohn JN, Tristani FE, Khatri IM: Cardiac and peripheral vascular effects of digitalis on clinical cardiogenic shock. Am Heart J 78:318–330, 1969
3. Cotten M, Stopp PE: Action of digitalis on the non-failing heart of the dog. Am J Physiol 192:114–120, 1958
4. Mason DT, Braunwald E, Karsh RB, et al: Studies on digitalis. X. Effects of ouabain on forearm vascular resistance and venous tone in normal subjects and in patients in heart failure. J Clin Invest 43:532–543, 1964
5. Ross J, Waldhausen JA, Braunwald E: Studies on digitalis. II. Extracardiac effects of venous return and on the capacity of the peripheral vascular bed. J Clin Invest 39:937–942, 1960
6. Ross J, Braunwald E, Waldhausen JA: Studies on digitalis. I. Direct effects on peripheral vascular resistance. J Clin Invest 39:930–936, 1960
7. Kwan-Gett CS, Wu Y, Collan R, et al: Total replacement artificial heart and driving system with inherent regulation of cardiac output. Trans Am Soc Artif Intern Organs 15:245–250, 1969
8. Lawson JH, Olsen DB, Hershgold E, et al: A comparison of polyurethane and silastic artificial hearts in 10 long survival experiments in calves. Trans Am Soc Artif Intern Organs 21: 368–373, 1975
9. Stanley TH, Liu W-S, Isern-Amaral J, et al: Periodic pulmonary shunt analysis as a method of optimizing cardiac output after artificial heart implantation. Trans Am Soc Artif Intern Organs 21:353–360, 1975
10. Liu W-S, Stanley TH, Isern-Amaral J, et al: Cardiovascular and respiratory effects of isoproterenol before and after artificial heart implantation. Anesth Analg 55:569–576, 1976
11. Stanley TH, Isern-Amaral J, Liu W-S, et al: Peripheral vascular versus direct cardiac effects of calcium. Anesthesiology 45:46–58, 1976
12. Williams MH, Zohman LR, Ratner AC: Hemodynamic effects of cardiac glycosides on normal human subjects during rest and exercise. J Appl Physiol 13:417–421, 1958
13. Momma K, Linde LM, Goldberg SJ, et al: Effects of cardiac glycosides on the abnormal pulmonary circulation of the dog. Am Heart J 79:87, 1970
14. Gould L, Lyon AF, Ettinger S, et al: The effect of stepwise dose of digitalis on hemodynamic function in man. Angiology 21: 468–485, 1970
15. Dock W, Trainer ML: The circulatory changes after full therapeutic doses of digitalis, with a critical discussion of views on cardiac output. J Clin Invest 8:467–484, 1930

16. Tainter ML, Dock W: Further observations on the circulatory actions of digitalis and strophanthus with special reference to the liver and comparisons with histamine and epinephrine. J Clin Invest 8:485-503, 1930
17. Katz LN, Rodbard S, Friend M, et al: The effects of digitalis on the anesthetized dog. I. Action on the splanchnic bed. J Pharmacol Exp Ther 62:1-15, 1938
18. Smith NT, Gershwin ME, Jurley EJ: Hemodynamic effects of ouabain in the surgically denervated, autotransplanted dog heart. Arch Int Pharmacodyn Ther 173:95-114, 1968
19. Smith TW: Digitalis glycosides. N Engl J Med 288:719-722, 1973
20. Harvey RM, Feuer MI, Cathcart RT, et al: Some effects of digoxin upon the heart and circulation in man. Am J Med 7: 439-453, 1949
21. Yoshida Y: Studies on the pathologic physiology of pulmonary hypertension in mitral valve disease. I. The role of the sympathetic nervous system on the increment of pulmonary vascular resistance. Jpn Circ J 33:359-376, 1969
22. Stanley TH, Liu W-S, Gentry S, et al: Blood and urine catecholamine concentrations after implantation of artificial heart. J Thorac Cardiovasc Surg 71:704-710, 1976
23. Gracey DR, Brandfonbrener M: The effect of lanatoside C on coronary vascular resistance. Am Heart J 66:88-94, 1963

---

## Determinants of Ventricular Defibrillation

Conventional defibrillators which stored no more than 400 J and used damped sine wave pulses defibrillated 240 of 253 (95%) episodes of ventricular fibrillation (VF) in 94 prospectively assessed resuscitations in 88 adults. Shocks of 80 to 240 J (under 3 J/kg) delivered to the chest wall defibrillated more often than higher energy levels. Defibrillation rate did not correlate with weight. Defibrillation was determined by the diagnosis and setting in which VF occurred. Patients with acute myocardial infarction (AMI) and primary VF or with coronary disease and no AMI defibrillated more easily than patients with AMI and secondary VF or with no coronary disease. VF in a terminal patient (agonal VF) defibrillated less often than VF in other clinical situations. Age, weight, delivered energy, duration of pulse wave, and duration of VF had little, if any, influence on rate of defibrillation. These data fail to support the use of more expensive, high-output defibrillators sold by some manufacturers. *(Gascho JA, Crampton RS, Cherwek ML, et al: Determinants of ventricular defibrillation in adults. Circulation 60:231-240, 1979)*

*See also*—Editorial *(Adgey AAJ, Patton JN, Campbell NPS, et al: Ventricular defibrillation: appropriate energy levels. Circulation 60:219-223, 1979).*

ANESTH ANALG
59:19-21, 1980

# Withdrawal Convulsions in Mice following Nitrous Oxide

Marilyn H. Harper, MD,* Peter M. Winter, MD,† Brynte H. Johnson, AB,‡ Donald D. Koblin, PhD,§ and Edmond I. Eger II, MD||

HARPER, M. H., WINTER, P. M., JOHNSON, B. H., KOBLIN, D. D., AND EGER, E. I., II: Withdrawal convulsions in mice following nitrous oxide. Anesth Analg 59:19–21, 1980.

Mice may be induced to convulse after (but not prior to) breathing nitrous oxide. We found that the incidence of this withdrawal phenomenon is related to the partial pressure of nitrous oxide. A minimum (threshold) value of about 0.5 atm is necessary and the majority of mice convulse following exposure to 0.9 atm or greater. Exposures of longer than 15 to 30 minutes do not significantly increase the incidence of convulsions at any given partial pressure. The mice remain susceptible to the induction of convulsions for only a brief period after removal from nitrous oxide. Although the duration of susceptibility is slightly increased after exposure to higher partial pressures, susceptibility in almost all cases is lost by 90 minutes. In mice, exposure to nitrous oxide is associated with evidence of physical dependence as evidenced by withdrawal symptoms, symptoms that may be related to the appearance of excitement which sometimes follows nitrous oxide anesthesia.

**Key Words:** ANESTHETICS, Gases: nitrous oxide; ANESTHETICS: tolerance; BRAIN: convulsions; BRAIN: delirium.

CHRONIC ingestion of sedative-hypnotics or alcohol may produce physical dependence in animals or humans. When dependence is established, a withdrawal reaction occurs upon abrupt discontinuance of drug ingestion. In mice, withdrawal is evidenced by convulsions that appear when the mouse is picked up by the tail.[1] We previously found that this characteristic withdrawal seizure also occurred after a short exposure to an anesthetizing partial pressure of nitrous oxide or after chronic (days to weeks) exposure to subanesthetic levels of nitrous oxide.[2] We also demonstrated withdrawal following brief exposure to anesthetizing levels of diethyl ether, cyclopropane, and ethylene.[3]

Since withdrawal signs had been produced by both short exposure to anesthetic levels of inhaled gases and prolonged exposure to subanesthetic levels, we sought to determine the time-dose relationship required to produce dependence. Either a simple partial pressure times duration of exposure relationship could exist or there could be a minimum partial pressure below which dependence is not produced even after prolonged exposure. Similarly, a minimum duration of exposure could be necessary or the effect could be primarily related to the partial pressure administered.

We therefore addressed the following questions. (1) Is there a threshold or minimum partial pressure required below which convulsions do not occur? (2) What is the minimum duration of exposure required at any given partial pressure? (3) Is the incidence of withdrawal convulsions related principally to partial pressure or to duration of exposure? (4) Does partial pressure or duration of exposure determine how long the dependent stage persists?

---

* Assistant Clinical Professor of Anesthesia, University of California.

† Professor of Anesthesiology, University of Washington. Present Address: University of Pittsburgh.

‡ Staff Research Associate, Department of Anesthesia, University of California.

§ Assistant Research Chemist, Department of Anesthesia, University of California.

|| Professor of Anesthesia, University of California.

Supported in part by United States Public Health Service grant 15571.

Received from the Department of Anesthesia, University of California, San Francisco, California 94143. Accepted for publication August 21, 1979.

Reprint requests to Dr. Harper, Veterans Administration Medical Center, 4150 Clement St, San Francisco, CA 94121.

## Methods

Groups of 10 to 14, 20- to 30-g, male Swiss ICR mice were exposed to nitrous oxide in a 20-L pressure chamber. The mice were placed in plastic cages with wire-mesh tops designed to contain three to six mice per section. No mouse was used in more than one test and no mouse displayed convulsions prior to anesthetic exposure.

The pressure chamber temperature was thermostatically regulated and maintained at 30–31 C. Chamber gases were mixed and pulled through carbon dioxide absorbent by an induction motor-driven fan. Samples of gas in the chamber were removed through a bleed valve and analyzed by gas chromatography.

The pressure chamber was flushed with oxygen for 10 minutes resulting in 100% oxygen at 1 atm. Nitrous oxide was then added to the desired partial pressure, which was 0.6, 0.7, 0.9, 1.2, or 1.6 atm of nitrous oxide. Loss of pressure in the chamber ranged from 0.5 to 1 psi/hr during all experiments. Exposure times at each partial pressure were 15, 30, 60, 120, 240, or 1,000 minutes. In addition, mice were exposed for 8 minutes to 0.9, 1.2, and 1.6 atm of nitrous oxide. Animals exposed to 1.6 atm for 1,000 minutes did not survive in sufficient numbers to warrant inclusion of their data.

Each animal was tested for convulsions 15 minutes after removal from the chamber and every 15 minutes thereafter until no convulsions occurred in two consecutive tests. The mice were gently lifted and held by the tail for 6 seconds. The test was considered negative if convulsions did not occur within that time.

Differences were examined for significance by chi square analysis. A one-tailed Fishers exact test was used to determine significant differences in duration of the withdrawal reaction; $p$ less than 0.05 was accepted as significant.

Three additional groups of mice were tested to determine whether the experimental methods contributed to the incidence of convulsions. Group 1 (six mice) was exposed to 10 atm of helium in 1 atm of oxygen for 30 minutes. Group 2 (six mice) was exposed to 20 atm of helium in 1 atm of oxygen for 30 minutes. Group 3 (12 mice) was exposed to 1.5 to 2.2 atm of oxygen for 1,000 minutes. Decompression for all groups was approximately 1 atm/min, a rate comparable to the decompression in our other experimental groups.

## Results

The percent of animals convulsing 15 minutes after removal from nitrous oxide usually increased with an increase in the partial pressure of nitrous oxide (Table). For any given time of exposure there were 59 possible comparisons of the incidence of convulsions (e.g., at 8 minutes there were three comparisons: 0 to 57.1; 0 to 61.5; and 57.1 to 61.5). A higher dose was associated with a higher incidence in 90% of such comparisons, 2% showed no difference, and 8% showed a decreased incidence.

The percent convulsing at any partial pressure did not increase significantly with exposure times longer than 30 minutes. The average of values (average incidence) obtained following 8 to 240 minutes of exposure at any given partial pressure did not differ from the values obtained after 1,000 minutes of exposure. The duration of the withdrawal reaction was variable and did not correlate well with exposure times at a given partial pressure (Fig 1).

The average percent convulsing was higher following 0.7 atm exposures than 0.6 atm exposures ($p < 0.01$). The 1.2 atm values were higher than the 0.9 atm values ($p < 0.05$). However, 0.7 and 0.9 atm values did not differ nor did the 1.2 and 1.6 atm values. Increasing the nitrous oxide partial pressure also prolonged the predisposition to convulsions (Fig 2) ($p < 0.005$).

None of the animals exposed to high pressures of helium and/or 100% oxygen displayed convulsions when removed from those gases.

## Discussion

Our results confirm those of earlier studies demonstrating that nitrous oxide produces dependence as evidenced by withdrawal convulsions.[2, 3] Although considerable variability exists, a dose relationship is clearly illustrated. The withdrawal response did not result from a simple product of partial pressure times exposure time. If the results we have obtained can be extrapolated to lower nitrous oxide partial pressures,

**TABLE**

**Percent of Animals Convulsing 15 Minutes after Removal from $N_2O$***

| Exposure time | Nitrous oxide | | | | |
|---|---|---|---|---|---|
| | 0.6 | 0.7 | 0.9 | 1.2 | 1.6 |
| *min* | | | *atm* | | |
| 8 | . . . | . . . | 0 | 57.1 | 61.5[b] |
| 15 | 7.1 | 28.6 | 71.4 | 35.7 | 50.0 |
| 30 | 28.6 | 50.0 | 35.7 | 71.4 | 92.9 |
| 60 | 7.1 | 37.7 | 42.9 | 85.7 | 91.7[a] |
| 120 | 21.4 | 42.9 | 57.1 | 71.4 | 100[a] |
| 240 | 7.1 | 7.4 | 75.0[a] | 75.0[a] | 70.0[c] |
| 1000 | 41.7 | 50.0[a] | 66.7[a] | 75.0[a] | . . . |

* N = 14 except as noted: *a*, N = 12; *b*, N = 13; *c*, N = 10.

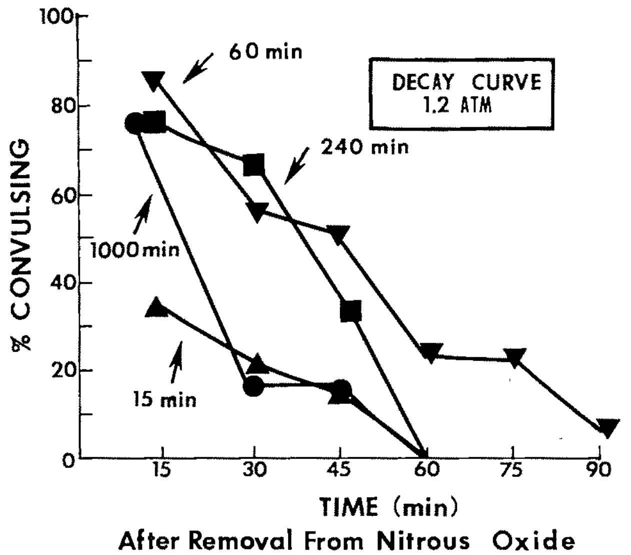


FIG 1. Duration of exposure to 1.2 atm of nitrous oxide did not have a significant effect on the rate at which the dependent stage dissipated. Convulsions did not persist longer than 90 minutes in any experimental group.

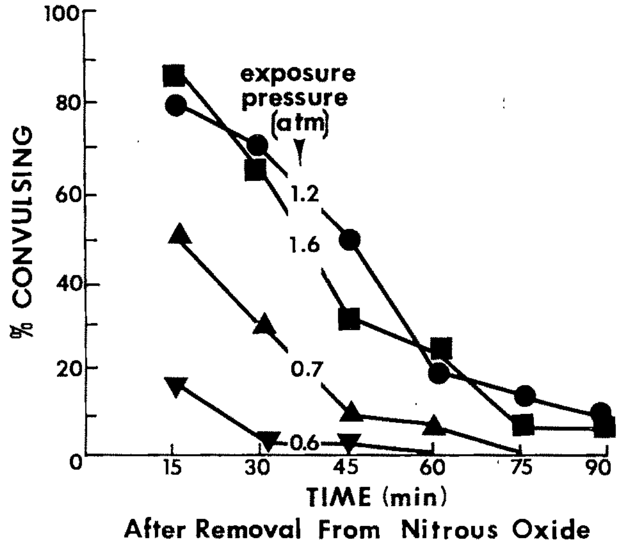


FIG 2. Average percent of animals convulsing following 30-, 60-, 120-, and 240-minute exposures was calculated for each nitrous oxide partial pressure. Higher partial pressures increased the duration of the withdrawal reaction ($p < 0.005$).

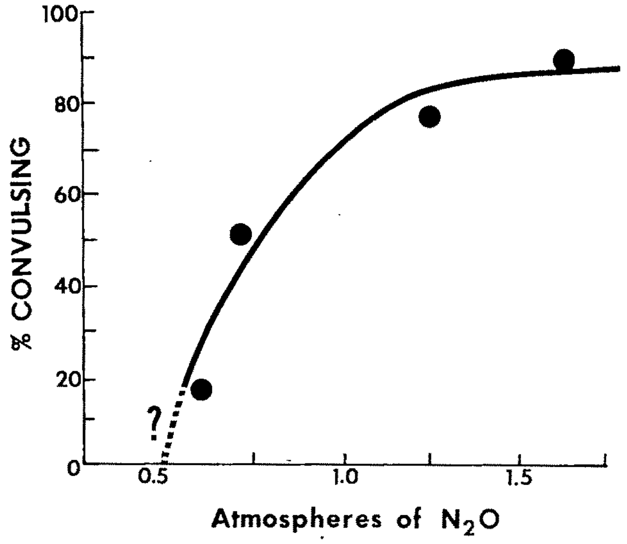


FIG 3. Extrapolation of the line formed from the summed results at each nitrous oxide partial pressure suggests that a threshold partial pressure of approximately 0.5 atm of nitrous oxide is necessary to produce withdrawal convulsions.

the threshold partial pressure would be about 0.5 atm (Fig 3). Other investigations support this conclusion. Of mice exposed to 0.5 atm of nitrous oxide for 3 weeks, 69% displayed convulsions 15 minutes after removal from nitrous oxide.[3] In contrast only 13% convulsed after a 3-week exposure to 0.4 atm of nitrous oxide.[3] We confirmed these results in subsequent studies and in addition found that 3-week exposures to 0.25 atm of nitrous oxide did not induce convulsions in any animal.[4]

The partial pressure of nitrous oxide used had a far greater impact on the incidence of convulsions than the duration of exposure. Although the withdrawal response occurred after 8 minutes of exposure to 1.2 and 1.6 atm of nitrous oxide, 15 to 30 minutes were required at 0.6, 0.7, and 0.9 atm. Continuing exposure beyond these times did not increase the incidence of convulsions at any concentration.

The dependent stage was rapidly reversible. That is, the withdrawal reaction did not persist longer than 90 minutes in any case. The duration of the withdrawal reaction also did not correlate with exposure times.

The rapid production of physical dependence by gaseous anesthetics may have clinical implications. The traditional view of postanesthetic delirium or excitement holds that those events result from stage II anesthesia.[5] Perhaps a withdrawal stage contributes to the severity of emergence delirium. The time course of recovery from withdrawal convulsions correlates well with the usual brevity of postanesthetic excitement.

## REFERENCES

1. Goldstein DB, Pal N: Alcohol dependence produced in mice by inhalation of ethanol: grading the withdrawal reaction. Science 172:288–290, 1971
2. Smith RA, Winter PM, Smith M, et al: Convulsions in mice after anesthesia. Anesthesiology 50:501–504, 1979
3. Smith RA, Winter PM, Smith M, et al: Tolerance to and dependence on inhalation anesthetics. Anesthesiology 50:505–509 1979
4. Koblin DD, Dong DE, Eger EI II: Tolerance of mice to nitrous oxide. J Pharmacol Exp Ther 211:317–325, 1979
5. Eckenhoff JE, Kneale DH, Dripps RD: Incidence and etiology of postanesthetic excitement. Anesthesiology 22:667–673, 1961

ANESTH ANALG
59:22-25, 1980

# Increased Skin Temperature during Transcutaneous Electrical Stimulation

**Stephen E. Abram, MD,* Caridad B. Asiddao, MD,* and Alan C. Reynolds, MD***

---

ABRAM, S. E., ASIDDAO, C. B., AND REYNOLDS, A. C.: Increased skin temperature during transcutaneous electrical stimulation. Anesth Analg 59:22-25, 1980.

Conflicting reports have appeared in the literature concerning the effects of transcutaneous electrical nerve stimulation on skin temperature. This report studied 33 patients with chronic pain involving one extremity (13 upper, 20 lower) to determine whether changes in sympathetic tone, as reflected in skin temperature, occurred in response to electrical stimulation of painful areas. Stimulation was carried out for 20 to 45 minutes. Skin temperatures were measured from the thumbs or great toes of stimulated and contralateral extremities before and during stimulation. Skin temperature rose 2.5 ± 0.7 C (mean ± SEM) in both the ipsilateral and contralateral extremity in patients who experienced relief of pain during stimulation. There was no significant change in skin temperature in patients who experienced no relief.

**Key Words:** PAIN: transcutaneous electrical stimulation; SYMPATHETIC NERVOUS SYSTEM: transcutaneous electrical stimulation.

---

THERE IS growing interest but considerable confusion concerning the effect of transcutaneous electrical stimulation on sympathetic nervous system activity. Owens et al[1] found small but consistent increases in skin temperature distal to ulnar nerve stimulation sites in volunteers. Stilz et al[2] reported clinical improvement and increased skin temperature following transcutaneous stimulation in a patient with sympathetic dystrophy. On the other hand, Ebersold et al[3] found no change in skin temperature during transcutaneous stimulation in either patients or volunteers. Other studies[4-6] have reported decreases in skin temperature during treatment.

The present study was undertaken to determine the short-term effects of transcutaneous electrical stimulation on sympathetic tone as evidenced by changes in cutaneous temperatures in patients with chronic pain.

## Methods

The effect of transcutaneous electrical stimulation on skin temperature was studied in 33 patients with chronic pain (at least 3 months duration) involving one extremity (20 lower, 13 upper). All patients had pain of nonmalignant origin. Diagnoses included chronic radiculopathy, sympathetic dystrophy, scar neuromata, diabetic neuropathy, and myofascial pain.

Transcutaneous electrical stimulation was carried out using Stimulation Technology (Stim Pulse), Medtronic (Neuromod) or Med General (Miniceptor) stimulators. Electrodes were placed over or adjacent to painful areas. Frequency was adjusted to maximum patient comfort, usually in the range of 75–100 Hz. Output was kept just below threshold for discomfort or motor stimulation (about 12 to 20 ma peak current at impedances of 1,200 to 1,300 Ω).

Temperature measurements were carried out using Yellow Springs thermometers with 5-mm thermistors. Output from thermometers was recorded on a dual-channel Brush recorder. Temperatures were recorded from the volar aspects of both thumbs during upper

---

* Assistant Professor.

Received from the Department of Anesthesiology Medical College of Wisconsin, 8700 W. Wisconsin Avenue, Milwaukee, Wisconsin 53226. Accepted for publication August 23, 1979.

Reprint requests to Dr. Abram.

extremity stimulation or the plantar aspects of the great toes during lower extremity stimulation. Ambient temperature was kept at 23 C. Baseline skin temperatures were recorded for at least 5 minutes prior to stimulation and for at least 20 minutes after stimulation was begun. Maximum change in skin temperature (positive or negative) was recorded in each patient on both the stimulated and nonstimulated extremity.

Patients rated pain relief as either none, slight, moderate, or considerable. Patients who rated their relief as none or slight were classified as having obtained no relief. Those rating relief as moderate to considerable were considered as having relief. Mean skin temperatures and standard errors in each of the two groups (relief and no relief) were determined on stimulated and nonstimulated extremities. In addition, the maximum temperature change and direction of change were recorded in both extremities for each patient, and the mean and standard error for these changes determined in both groups.

## Results

Prior to stimulation there was no significant difference in cutaneous temperature between those patients who experienced relief and those who did not. The maximum increase in skin temperature on the stimulated side averaged 2.5 C in the 15 patients who experienced pain relief during stimulation. A similar increase in mean skin temperature was noted on the unstimulated side (+2.5 C). These changes in skin temperature were statistically significant (Table 1). Mean temperatures recorded at 5-minute intervals rose in both extremities for 15 minutes, then began to level off (Figure).

There was little difference in temperature response between patients with upper and lower extremity pain. The mean increase in temperature in patients with upper extremity pain was +2.0 C on the stimulated side and +2.3 C on the contralateral side. The mean increase in temperature in patients with lower extremity pain was +2.9 C on the stimulated side and +2.6 C on the contralateral side.

In the 18 patients who did not experience pain relief, there was no significant change in skin temperature during stimulation (Table 1 and Figure). Ten of the 15 patients who had relief during stimulation demonstrated an increase in skin temperature of 1 C or more; three of the 18 patients who had no relief experienced such a rise.

Several patients who had pain relief associated with stimulation had dramatic increases in temperature during stimulation (up to 7.5 C). In such patients, temperatures began to rise within 10 minutes of onset of stimulation, peaked 10 to 15 minutes after stimulation was begun, and slowly fell toward prestimulation levels over the next 10 to 15 minutes despite continued stimulation and relief. Almost all pronounced increases in temperature occurred bilaterally. However, in one patient with chronic foot pain of undetermined etiology skin temperature on the contralateral side increased markedly but, despite relief of pain, failed to change on the stimulated side.

Pain relief began within 10 minutes of the onset of stimulation in most patients who obtained relief, and

**TABLE 1**

**Mean Skin Temperatures (±SEM) before and during Transcutaneous Electrical Stimulation in Patients with and without Relief of Pain**

| | Mean temperature (C) before stimulation | Mean temperature (C) at time of maximum change | Mean change in maximum temperature (C) |
|---|---|---|---|
| Relief (N = 15) | | | |
| Stimulated extremity | 28.8 ± 0.9 | 31.2 ± 0.9 | +2.5 ± 0.7<br>($p < 0.005$)* |
| Nonstimulated extremity | 29.4 ± 0.9 | 31.9 ± 0.9 | +2.5 ± 0.7<br>($p < 0.005$) |
| No relief (N = 18) | | | |
| Stimulated extremity | 28.6 ± 0.9 | 28.4 ± 1.0 | −0.2 ± 0.9<br>(NS) |
| Nonstimulated extremity | 28.6 ± 0.9 | 28.6 ± 1.0 | −0.2 ± 0.4<br>(NS) |

* Paired *t*-test.

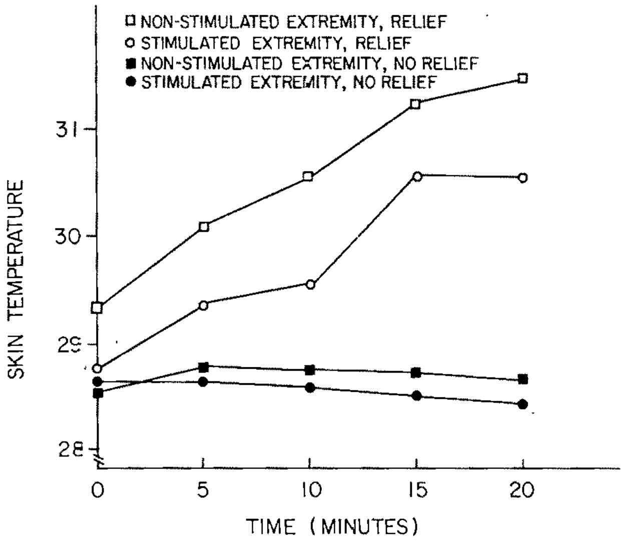


FIGURE. Mean cutaneous temperatures (C) before and during transcutaneous electrical stimulation in 33 patients (15 with relief of pain, 18 with no relief).

usually lasted several hours. Relief outlasted the period of stimulation in all patients.

The two groups of patients (relief and no relief) were of comparable age; duration of pain and sites of pain were also comparable (see Table 2). The large majority of patients relieved of pain by stimulation were women. Both groups contained a variety of chronic pain problems, including sympathetic dystrophy (five in the relief group, 10 in the no relief group). This diagnosis was based on the quality of pain and the existence of various physical stigmata, including hyperesthesia, trophic skin changes, vasoconstriction, edema, cyanosis, and hyperhydrosis. Several patients in both groups had obtained transient pain relief in the past from sympathetic blocks. There was no correlation between diagnosis and changes in skin temperature during stimulation.

## Discussion

The results of this study indicate that, in certain patients, stimulation-induced analgesia is associated with diminished sympathetic tone, as evidenced by increased skin temperature. Such changes are not confined to the stimulated extremity, but are generally of equal magnitude in the contralateral extremity. On the basis of these data, it is impossible to determine a cause and effect relationship between stimulation-induced analgesia and diminished sympathetic activity. Beneficial effects in some patients may result from a generalized, stimulation-induced loss of sympathetic tone. Alternatively, diminished sympathetic activity could represent elimination of pain-induced vasoconstriction as stimulation-induced analgesia begins, i.e., vasodilation secondary to pain relief.

A number of mechanisms have been proposed to explain how transcutaneous electrical stimulation produces analgesia. Both selective stimulation of large afferent fibers[7] and blockade of small fiber activity[8] have been suggested. Either mechanism could act to diminish pain perception through a dorsal horn gate control mechanism.[9] Melzack[7] suggests that stimulation of small afferent fibers may activate brainstem centers which exert descending inhibitory effects on pain transmission.

There is also a possibility that electrical stimulation blocks sympathetic activity peripherally or centrally in certain patients. The resultant sympathetic blockade may be responsible for analgesia produced. Procacci et al[10] demonstrated changes in cutaneous pain thresholds and sympathogalvanic reflexes in both blocked and contralateral extremities following sympathetic blockade. They suggested that efferent sympathetic discharge is under the control of ipsilateral and contralateral neuronal systems located at different levels of the central nervous system and that any change in afferent input sets up variations of sympathetic discharge through reflexes at various levels. Thus, modulation of afferent input through electrical stimulation may block sympathetic discharge at one or several levels of the neuraxis. The diminished sympathetic activity could provide pain relief, particularly in reflex sympathetic dystrophies.

Conflicting reports[2, 3, 5, 6] on the effect of transcutaneous electrical stimulation on skin temperature are probably due to two factors. First, there may be differences in response based upon differences in the characteristics of the electrical stimuli, including voltage, frequency, pulse width, and wave form. Most studies, including this one, did not attempt to standardize these variables. Second, different types of patients have been examined in the studies cited. Ignelzi et al[6] noted significant decreases in skin temperature during stimulation in patients with degenerative spine disease or peripheral nerve injury but also noted peripheral warming during stimulation in some patients with causalgia. Our inability to correlate warming with diagnosis perhaps illustrates the difficulty in diagnosing long-standing pain problems.

Evidence is accumulating that transcutaneous electrical stimulation is effective in treating chronic painful states associated with sympathetic hyperactivity. This study offers further evidence that this form of treatment may reduce sympathetic tone in certain patients. Based on our data, decreased sympathetic outflow more frequently occurs in patients who obtain pain relief during stimulation than in patients in whom pain is not relieved by stimulation.

**TABLE 2**

**Physical Data of Patients Who Experienced Relief from Transcutaneous Electrical Nerve Stimulation and Those Who Did Not**

| | Relief (N = 15) | No relief (N = 18) |
|---|---|---|
| Mean age | 49 | 46 |
| Males/females | 2/13 | 8/10 |
| Upper extremity pain | 7 | 6 |
| Lower extremity pain | 8 | 12 |
| Mean duration of symptoms | 3 yr, 4 mo | 3 yr, 1 mo |

### REFERENCES

1. Owens S, Atkinson ER, Lees DE: Thermographic evidence of reduced sympathetic tone with transcutaneous nerve stimulation. Anesthesiology 50:62–65, 1979

2. Stilz RJ, Carron H, Sanders DB: Reflex sympathetic dystrophy in a 6-year old: successful treatment by transcutaneous nerve stimulation. Anesth Analg 56:438–443, 1977
3. Ebersold MJ, Laws ER, Albers JW: Measurement of autonomic function before, during and after transcutaneous stimulation in patients with chronic pain and in control subjects. Mayo Clin Proc 52:228–232, 1977
4. Abram SE: Increased sympathetic tone associated with transcutaneous electrical stimulation. Anesthesiology 45:575–577, 1976
5. Callaghan M, Sternbach RA, Nyquist JK, et al: Changes in somatic sensitivity during transcutaneous electrical analgesia. Pain 5:115–127, 1978
6. Ignelzi RJ, Sternbach RA, Calaghan M: Somatosensory changes during transcutaneous electrical analgesia, in Advances in Pain Research and Therapy, Vol 1. Edited by JJ Bonica and D Albe-Fessard. New York, Raven Press, 1976, pp 421–425
7. Melzack R: Guest discussion. Anesth Analg 56:442–443, 1977
8. Campbell JN, Laub A: Local analgesia from percutaneous electrical stimulation. Arch Neurol 28:347–350, 1953
9. Melzack R, Wall PD: Pain mechanisms: a new theory. Science 150:971–979, 1965
10. Procacci P, Francini F, Zoppi M, et al: Role of sympathetic system in reflex dystrophies, in Advances in Pain Research and therapy, Vol 1. Edited by JJ Bonica and D Albe-Fessard. New York, Raven Press, 1976, pp 953–957

---

## Neuromuscular Transmission in Thyrotoxicosis

The incidence of thyrotoxicosis in patients with myasthenia gravis is estimated as 5.3% but the incidence of myasthenia gravis in the course of thyrotoxicosis is only 0.2%. The association between these two diseases does not appear to be a chance one, and there are two suggested basic mechanisms. There is either an action of thyroid hormone on the neuromuscular junction or the existence of a cause common to both. The fatigability seen clinically in thyrotoxic myopathy could be partly attributed to myasthenia. With these possibilities in mind a search for electromyographic stigmata of latent myasthenia was undertaken in 48 consecutive patients with hyperthyroidism who also had chronic myopathy. Eight patients had abnormal neuromuscular transmission, as in myasthenia gravis, and one of these patients later developed clinical myasthenia involving the ocular muscles. Three other patients showed abnormal facilitation, as in the Eaton-Lambert syndrome. *(Puvanendran K, Cheah JS, Naganathan N: Neuromuscular transmission in thyrotoxicosis. J Neurol Sci 43:47–57, 1979)*

ANESTH ANALG
59:26-30, 1980

# Cardiovascular and Neuromuscular Effects of Org NC 45, Pancuronium, Metocurine, and *d*-Tubocurarine in Dogs

**Leo H.D.J. Booij, MD,* Robert P. Edwards, MD,† Yung J. Sohn, MD,‡ and Ronald D. Miller, MD§**

BOOIJ, L.H.D.J., EDWARDS, R. P., SOHN, Y. J., AND MILLER, R. D.: Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine, and *d*-tubocurarine in dogs. Anesth Analg 59:26-30, 1980.

We compared the cardiovascular and neuromuscular effects of Org NC 45 with those of pancuronium, metocurine, and *d*-tubocurarine in six dogs anesthetized with halothane. The $ED_{90}$ (dose of drug which produced a 90% depression of twitch tension) of Org NC 45, pancuronium, metocurine, and *d*-tubocurarine was 14 ± 3, 22 ± 3, 63 ± 19, and 130 ± 19 μg/kg, respectively. All subsequent neuromuscular and cardiovascular effects were determined from a dose equal to 3 times the $ED_{90}$ of muscle relaxant. Org NC 45, pancuronium, metocurine, and *d*-tubocurarine produced a neuromuscular blockade with a duration (time from relaxant administration until recovery of 50% of the original twitch tension) of 42 ± 2, 108 ± 10, 109 ± 21, and 100 ± 19 minutes, respectively. Org NC 45 caused no significant cardiovascular changes. Pancuronium increased heart rate, mean arterial blood pressure, cardiac output, and pulmonary wedge pressure, and it decreased systemic vascular resistance ($p < 0.05$). Although metocurine also increased heart rate and cardiac output ($p < 0.05$), mean arterial blood pressure and pulmonary wedge pressure did not change. *d*-Tubocurarine decreased all cardiovascular parameters except heart rate which increased significantly ($p < 0.05$). We conclude that Org NC 45 produces a neuromuscular blockade of shorter duration with fewer cardiovascular changes than that of pancuronium, metocurine, or *d*-tubocurarine.

**Key Words:** NEUROMUSCULAR RELAXANTS: pancuronium, metocurine, *d*-tubocurarine, Org NC 45.

A HOMOLOGUE of pancuronium, Org NC 45 (Fig. 1) has been found to produce a neuromuscular blockade of shorter duration with fewer autonomic changes than that of pancuronium in the cat.[1] In this study, we compared the cardiovascular and neuromuscular effects of Org NC 45 with pancuronium, metocurine, and d-tubocurarine in anesthetized dogs using each dog as its own control.

## Methods

Six dogs, each weighing 13 to 21 kg, were anesthetized by inhalation of halothane and oxygen. The

---

* Senior Clinical and Research Associate; Visiting Professor in San Francisco during study.

† Assistant Professor.

‡ Associate Professor.

§ Professor.

Supported by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.)-NATO Grant; Organon, Inc, Oss, Netherlands; and the Anesthesia-Pharmacology Research Foundation.

Received from the Departments of Anesthesia and Pharmacology, University of California, San Francisco, San Francisco, California 94143. Accepted for publication August 24, 1979. Presented in part at the 1979 Annual Meeting of the American Society of Anesthesiologists, San Francisco.

Reprint requests to Dr. Miller, Department of Anesthesia (436S).

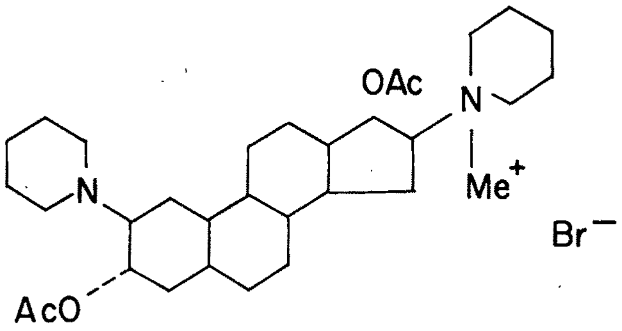


FIG 1. Formula of Org NC 45.

end-tidal halothane concentration was maintained at 1.25 ± 0.05%. After endotracheal intubation without the use of other drugs, ventilation was controlled to maintain $Pa_{CO_2}$ between 32 and 40 torr. The electrocardiogram was continuously recorded. A catheter was inserted percutaneously into the right femoral artery from which arterial blood pressure was transduced (model P2306, Statham Instruments) continuously and printed on a Grass recorder. A triple-lumen Swan-Ganz catheter was inserted into the pulmonary artery via the right femoral vein from which central venous pressure (CVP) and pulmonary wedge pressure (PWP) were measured. Cardiac output was measured in duplicate by a thermodilution method using an Edwards 9520 cardiac output computer. Systemic vascular resistance (SVR) was calculated [SVR = (mean arterial pressure − CVP)/cardiac output]. Other than halothane, all drugs were administered via an indwelling catheter in a vein in the left front leg. Supramaximal stimuli, 0.15 Hz and 0.2-msec duration, were delivered to the left sciatic nerve through electrodes inserted percutaneously. The resultant twitches of the foot were quantitated by a Grass F10 force displacement transducer and recorded on a Grass polygraph. After all parameters had been constant for at least 1 hour, dose-response curves using the incremental-cumulative method of Donlon et al[2] were determined for Org NC 45, pancuronium, d-tubocurarine, and metocurine. From these curves, the $ED_{90}$ (that dose of relaxant which resulted in a 90% depression of twitch tension) were derived.[2] After the control twitch height was stable the muscle relaxant to be studied was given in small increments. When the peak response to the initial dose had been obtained, a second dose was given and the subsequent peak response then determined. This was repeated until 95 to 99% depression of twitch tension occurred. Three to six doses were required. The sequence lasted between 10 and 15 minutes. When the twitch had returned to its original tension and cardiovascular parameters had been constant for at least 1 hour, a dose of neuromuscular relaxant equal to 3 times the $ED_{90}$ was administered as an intravenous bolus. Cardiovascular parameters were determined and recorded 1 minute before and 2, 5, 10, 20, 30, 40, 50, 60, 70, and 80 minutes after administration of 3 times the $ED_{90}$ dose of muscle relaxant. Only one neuromuscular relaxant was studied with each anesthetic administration. Each dog was studied with each relaxant at an interval of at least 1 week. The order of muscle relaxant administration for each dog was randomized. Duration of neuromuscular blockade produced by 3 times $ED_{90}$ dose was determined and defined as that time from relaxant administration until recovery of 50% of the original twitch tension. The data were analyzed by analysis of covariance and Sheffe's multiple contrast procedure.[3]

## Results

We found Org NC 45 was about 1.6, 4.5, and 9.3 times more potent than pancuronium, metocurine, and *d*-tubocurarine, respectively (Table). There was no significant difference in the duration of neuromuscular blockade between pancuronium, metocurine, and *d*-tubocurarine after administration of 3 times the $ED_{90}$ dose (Table). However, the duration of neuromuscular blockade from Org NC 45 was significantly shorter than that of the other neuromuscular relaxants ($p < 0.01$) (Table).

Control cardiovascular values during halothane anesthesia, but before neuromuscular relaxant administration included: heart rate 94 ± 5 (SE) beats/min, mean arterial blood pressure 110 ± 4 torr, cardiac output 2.1 ± 0.3 L/min, PWP 11 ± 1 torr, SVR 38 ± 4 units, and CVP 4 ± 1 torr. There was no significant difference in the control cardiovascular parameters between muscle relaxant groups. All values after administration of the relaxant were converted to percent of control.

**TABLE**

**Neuromuscular Effects of Org NC 45, Pancuronium, Metocurine and *d*-Tubocurarine (mean ± SE)**

| | Org NC 45 | Pancuronium | Metocurine | *d*-Tubocurarine |
|---|---|---|---|---|
| $ED_{90}$* (μg/kg) | 14 ± 3 | 22 ± 3 | 63 ± 19 | 130 ± 19 |
| Duration† (min) | 42 ± 2 | 108 ± 10 | 109 ± 21 | 100 ± 19 |

* Dose which results in a 90% depression of twitch tension.

† Time from administration of 3 times the $ED_{90}$ of each relaxant until recovery of 50% of the original twitch tension.

Three times the $ED_{90}$ dose of Org NC 45 caused no significant cardiovascular changes. Pancuronium increased heart rate (Fig 2), mean arterial blood pressure (Fig 3), cardiac output (Fig 4) and PWP (Fig 5), and decreased SVR (Fig 6) ($p < 0.05$). Although CVP (Fig 7) tended to increase following pancuronium, the changes were insignificant. Metocurine also increased in heart rate and cardiac output (Figs 2 and 4) ($p < 0.05$); however, mean arterial blood pressure and PWP did not change (Figs 3 and 5). SVR and CVP decreased, although the latter was transient (Figs 6 and 7). *d*-Tubocurarine decreased all cardiovascular parameters except heart rate which was significantly increased (Fig 2) ($p < 0.01$). The decrease in cardiac output was transient and ultimately increased 30 minutes after d-tubocurarine administration (Fig 4).

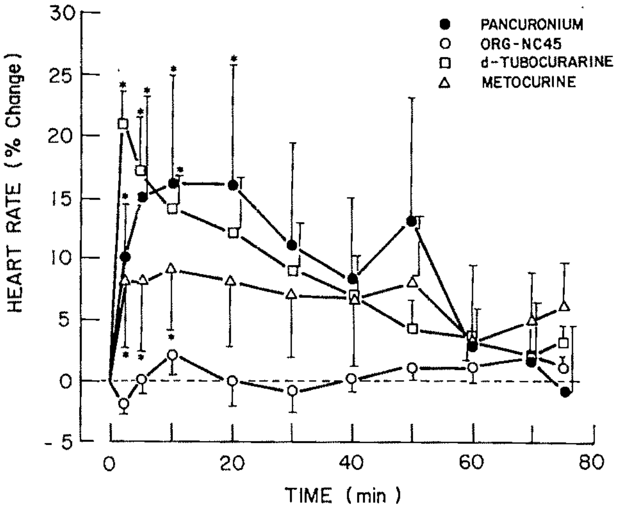


FIG 2. Effect of Org NC 45, 42 μg/kg, pancuronium, 66 μg/kg, metocurine, 189 μg/kg, and *d*-tubocurarine, 390 μg/kg, intravenously on percent change in heart rate. These doses are 3 times the $ED_{90}$. ($ED_{90}$ is that dose required to depress twitch tension 90%.) Each symbol and bracket represents the mean ± 1 SE in six dogs. Asterisk indicates a significant difference from the predrug heart rate.

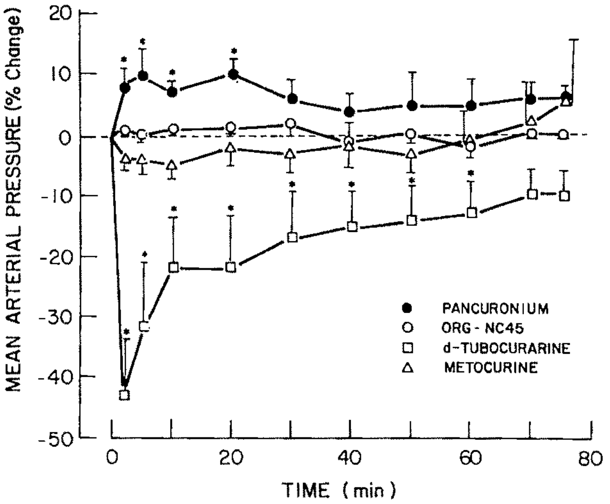


FIG 3. Effect of Org NC 45, 42 μg/kg, pancuronium, 66 μg/kg, metocurine, 189 μg/kg, and *d*-tubocurarine, 390 μg/kg, intravenously on percent change in mean arterial blood pressure. These doses are 3 times the $ED_{90}$. ($ED_{90}$ is that dose required to depress twitch tension 90%.) Each symbol and bracket represents the mean ± 1 SE in six dogs. Asterisk indicates a significant difference from the predrug mean arterial blood pressure.

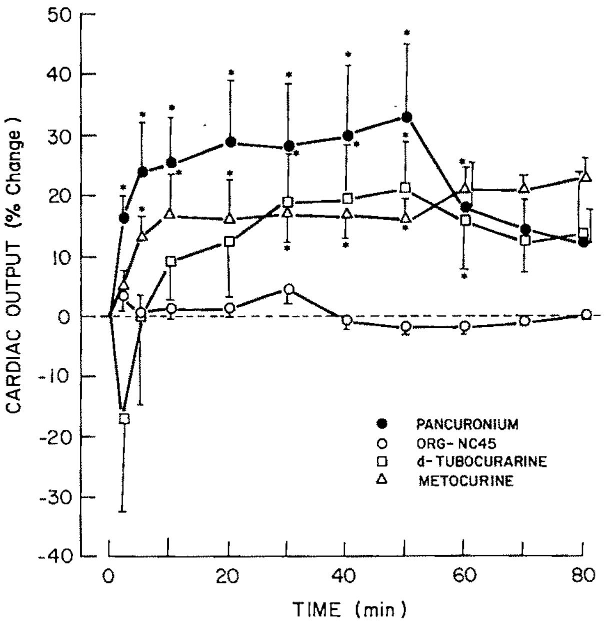


FIG 4. Effect of Org NC 45, 42 μg/kg, pancuronium, 66 μg/kg, metocurine, 189 μg/kg, and *d*-tubocurarine, 390 μg/kg, intravenously on percent change in cardiac output. These doses are 3 times the $ED_{90}$. ($ED_{90}$ is that dose required to depress twitch tension 90%). Each symbol and bracket represents the mean ± 1 SE in six dogs. Asterisk indicates a significant difference from the predrug cardiac output.

## Discussion

A major problem in comparing circulatory effects of neuromuscular relaxants is the failure to study equipotent neuromuscular blocking doses. For endotracheal intubation and maintenance of adequate surgical relaxation, doses larger than the $ED_{90}$ frequently are administered.[4] Since our study was designed to accentuate any cardiovascular effects of the neuromuscular relaxants, we studied a dose 3 times the $ED_{90}$ which we presume is an equipotent neuromuscular blocking dose.

In contrast to other neuromuscular relaxants, a large dose of Org NC 45 produced no significant cardiovascular changes. We found that pancuronium produced the well documented tachycardia, increase in blood pressure, and PWP.[5] Consistent with the studies

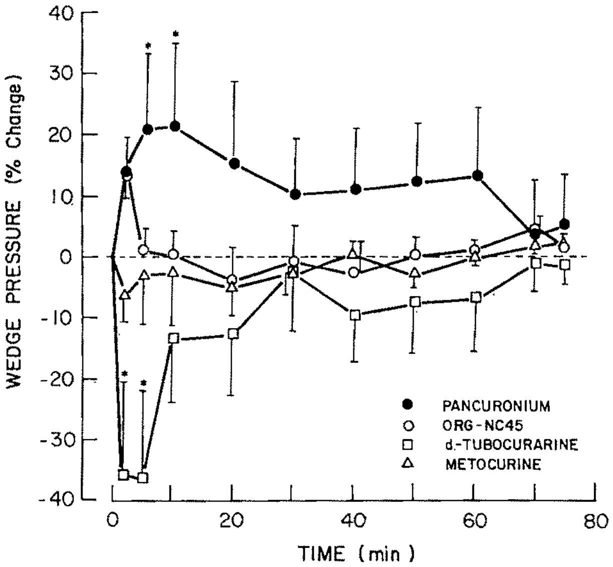


Fig 5. Effect of Org NC 45, 42 μg/kg, pancuronium, 66 μg/kg, metocurine, 189 μg/kg, and *d*-tubocurarine, 390 μg/kg, intravenously on percent change in wedge pressure. These doses are 3 times the ED$_{90}$. (ED$_{90}$ is that dose required to depress twitch tension 90%.) Each symbol and bracket represents the mean ± 1 SE in six dogs. Asterisk indicates a significant difference from the predrug wedge pressure.

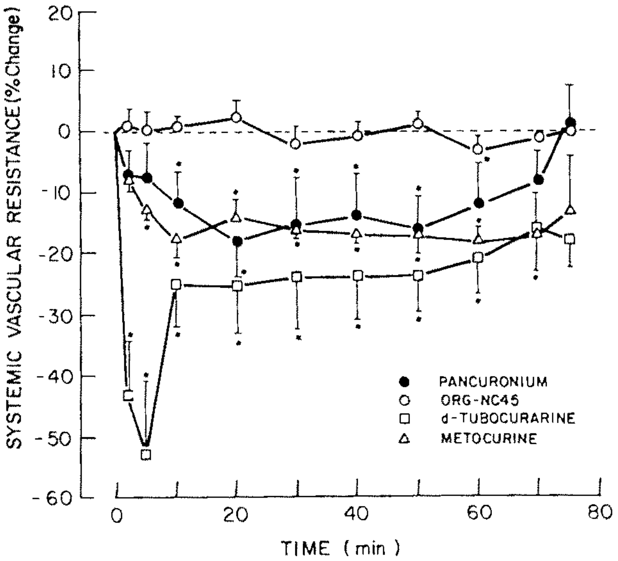


Fig 6. Effect of Org NC 45, 42 μg/kg, pancuronium, 66 μg/kg, metocurine, 189 μg/kg, and *d*-tubocurarine, 390 μg/kg, intravenously on percent change in systemic vascular resistance. These doses are 3 times the ED$_{90}$. (ED$_{90}$ is that dose required to depress twitch tension 90%.) Each symbol and bracket represents the mean ± 1 SE in six dogs. Asterisk indicates a significant difference from the predrug systemic vascular resistance.

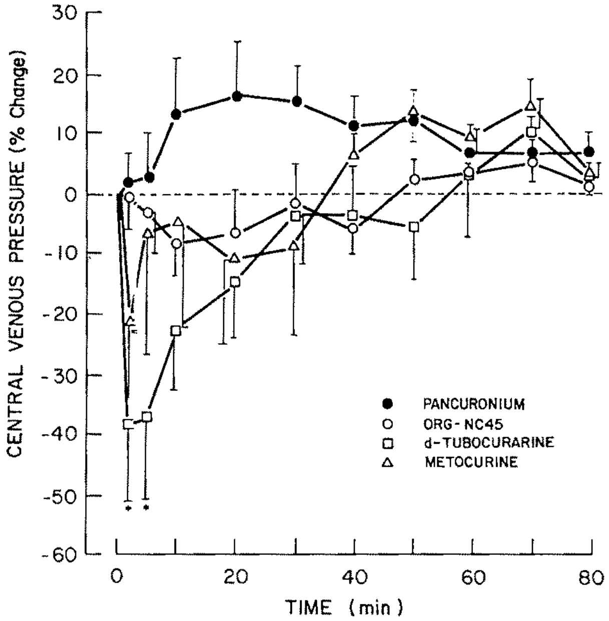


Fig 7. Effect of Org NC 45, 42 μg/kg, pancuronium, 66 μg/kg, metocurine, 189 μg/kg, and *d*-tubocurarine, 390 μg/kg, intravenously on percent change in central venous pressure. These doses are 3 times the ED$_{90}$. (ED$_{90}$ is that dose required to depress twitch tension 90%.) Each symbol and bracket represents the mean ± 1 SE in six dogs. Asterisk indicates a significant difference from the predrug central venous pressure.

of Stanley and Liu,[6] we found that pancuronium decreased SVR. In contrast, Stoelting[7] found that pancuronium did not change SVR. Other than species difference, we cannot explain the difference between our results and those of Stoelting.[7] In any event, these results are consistent with investigations that show that pancuronium produces tachycardia primarily by a vagolytic effect,[5, 8, 9] and secondly by a sympathomimetic effect.[10–12]

Metocurine caused a slight but significant increase in heart rate and cardiac output, a decrease in SVR and no change in mean arterial blood pressure. Generally, metocurine produces little or no cardiovascular changes. However, with large doses, increases in heart rate[4] and cardiac output,[13] and decreases in SVR[13] have been noted; this is consistent with the results of our study. In contrast, *d*-tubocurarine predictably depressed all cardiovascular parameters except heart rate, which increased. Hypotension and a slight tachycardia are consistent with the data of most studies,[14] although Hughes[15] found that *d*-tubocurarine decreased heart rate in dogs; however, this model is suspect because the control heart rate was 186 beats/min, which is unusually high. Furthermore, administration of atropine and gallamine in that study did not cause an increase in heart rate.[15] Of prime importance is the fact that Org NC 45 produced none of the cardiovascular changes associated with administration of other neuromuscular relaxants.

Org NC 45 appears to produce a neuromuscular blockade which is significantly shorter than that produced by the other neuromuscular relaxants tested; the reason for this is unknown (Table). Although we waited for at least 1 hour after complete recovery of twitch tension from initial $ED_{90}$ dose before giving 3 times the $ED_{90}$ dose, a cumulative effect could have been present. In spite of this limitation, Org NC 45 clearly has a shorter duration of action than that of the other relaxants tested.

In summary, the lack of significant cardiovascular effects and short duration of action support the decision to proceed with clinical trials with Org NC 45.

## ACKNOWLEDGMENTS

The authors acknowledge the advise of Philip L. Wilkinson, M.B., B.S., concerning cardiovascular measurements and the editorial advice of Dorothy Urban.

## REFERENCES

1. Durant NN, Marshall IG, Savage DS, et al: The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45 and other pancuronium analogues in the cat. J Pharm Pharmacol, in press 1979
2. Donlon JV, Ali HH, Savarese JJ: A new approach to the study of four nondepolarizing relaxants in man. Anesth Analg 53: 934-939, 1974
3. Neter J, Wasserman W: Applied Linear Statistical Models. Homewood, Ill, R.D. Irwin Co, 1975, pp 160-165, 689-703, 436-450, 480-482
4. Savarese JJ, Ali HH, Antonio RP: The clinical pharmacology of metocurine: dimethyltubocurarine revisited. Anesthesiology 47:277-284, 1977
5. Miller RD, Eger EI II, Stevens WC, et al: Pancuronium-induced tachycardia in relation to alveolar halothane, dose of pancuronium and prior atropine. Anesthesiology 42:352-355, 1975
6. Stanley TH, Liu WS: Cardiovascular effects of meperidine-$N_2O$ anesthesia before and after pancuronium. Anesth Analg 56:669-673, 1977
7. Stoelting RK: The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. Anesthesiology 36: 612-615, 1972
8. Saxena PR, Bonta IL: Mechanism of selective cardiac vagolytic action of pancuronium bromide: specific blockade of cardiac muscarinic receptors. Eur J Pharmacol 11:322-341, 1970
9. Gardier RW, Tsevdos EJ, Jackson DB: The effect of pancuronium and gallamine on muscarinic transmission in the superior cervical ganglion. J Pharmacol Exp Ther 204:46-53, 1978
10. Seed RF, Chamberlain JH: Myocardial stimulation by pancuronium bromide. Br J Anaesth 49:401-407, 1977
11. Domenech JS, Garcia RC, Sasian JMR, et al: Pancuronium bromide: an indirect sympathomimetic agent. Br J Anaesth 48: 1143-1148, 1976
12. Ivankovich AD, Miletich DJ, Albrecht RF, et al: The effect of pancuronium on myocardial contraction and catecholamine metabolism. J Pharm Pharmacol 27:837-841, 1975
13. Zaidan J, Philbin DM, Antonio RP, et al: Hemodynamic effects of metocurine in patients with coronary artery disease receiving propranolol. Anesth Analg 56:255-259, 1977
14. Munger WL, Miller RD, Stevens WC: The dependence of d-tubocurarine-induced hypotension on alveolar concentration of halothane, dose of d-tubocurarine, and nitrous oxide. Anesthesiology 40:442-448, 1974
15. Hughes R: Haemodynamic effects of tubocurarine, gallamine and suxamethonium in dogs. Br J Anaesth 42:928-934, 1970

ANESTH ANALG
59:31-34, 1980

# Antagonism of Org NC 45 Neuromuscular Blockade by Neostigmine, Pyridostigmine, and 4-Aminopyridine

**Leo H.D.J. Booij, MD,* Francien van der Pol,† Jan F. Crul, MD, PhD,‡ and Ronald D. Miller, MD§**

---

BOOIJ, L.H.D.J., VAN DER POL, F., CRUL, J. F., AND MILLER, R. D.: Antagonism of Org NC 45 neuromuscular blockade by neostigmine, pyridostigmine, and 4-aminopyridine. Anesth Analg 59:31-34, 1980.

The antagonism of Org NC 45 neuromuscular blockade by neostigmine, pyridostigmine, 4-aminopyridine, and their combinations was studied in the in vivo rat sciatic nerve anterior tibialis preparation using the constant infusion of Org NC 45 technique. The $ED_{50}$ (dose of drug which produced a 50% antagonism) of neostigmine, pyridostigmine, and 4-aminopyridine were 14.5, 75, and 466 $\mu$g/kg, respectively. The addition of 100 $\mu$g/kg of 4-aminopyridine, which produced no antagonism by itself, decreased neostigmine $ED_{50}$ to 9.8 $\mu$g/kg. The addition of 200 $\mu$g/kg of 4-aminopyridine, which produced a 14.8% antagonism by itself, decreased the $ED_{50}$ of pyridostigmine to 17.5 $\mu$g/kg. We concluded that neostigmine, pyridostigmine, and 4-aminopyridine effectively antagonize an Org NC 45 neuromuscular blockade. Neostigmine and pyridostigmine interact with 4-aminopyridine in a synergistic manner. The doses of antagonists were very similar to those required to antagonize a pancuronium neuromuscular blockade.

**Key Words:** NEUROMUSCULAR RELAXANTS: Org NC 45; antagonists, Neuromuscular relaxants: neostigmine, pyridostigmine, 4-aminopyridine.

---

A HOMOLOGUE of pancuronium, Org NC 45 produces a neuromuscular blockade which is shorter in duration (time from injection until 50% recovery) than that produced by an equi-potent dose of pancuronium.[1] Org NC 45 administered to dogs anesthetized with halothane produces essentially no change in blood pressure or heart rate whereas *d*-tubocurarine causes hypotension and pancuronium causes tachycardia.[1] The clinical usefulness of Org NC 45 will also depend on the ability of neostigmine and pyridostigmine to antagonize the neuromuscular blockade it produces. Recently, 4-aminopyridine has been advocated as an antagonist to non-depolarizing relaxants because it does not require concomitant administration of atropine and because it antagonizes neuromuscular blockades produced by many antibiotics.[2-4] However, 4-aminopyridine alone has limited clinical possibilities because of central nervous system stimulation. Miller et al[5,6] have found that very small doses of 4-aminopyridine markedly potentiate neostigmine and pyridostigmine when antago-

---

* Senior Clinical and Research Associate.

† Research Associate.

‡ Professor and Chairman of Anaesthesiology.

§ Professor of Anesthesia and Pharmacology, University of California, San Francisco; Visiting Professor in the Netherlands during part of the study.

Supported in part by Organon, Inc, Oss, Netherlands; and the Anesthesia-Pharmacology Research Foundation.

Received from the Institute of Anaesthesiology, Catholic University, Nijmegen, The Netherlands. Accepted for publication August 24, 1979.

Reprint requests to Dr. Miller, Department of Anesthesia 436S, University of California, San Francisco, CA 94143.

nizing pancuronium, therefore suggesting that the combination of neostigmine and 4-aminopyridine may be better than either drug alone. Accordingly, in the present study we determined the ability of neostigmine, pyridostigmine, and 4-aminopyridine alone and in combination to antagonize an Org NC 45 neuromuscular blockade in an in vivo rat sciatic nerve tibialis anterior muscle preparation.

## Methods

Seventy-five rats, 280 and 320 g each, were anesthetized with pentobarbital, 4 mg/100 g, and urethane, 50 mg/100 g, intraperitoneally. Both jugular veins were cannulated for administration of drugs. A carotid artery was cannulated for measurement and recording of arterial blood pressure. The trachea was intubated and ventilation controlled by means of a Braun air pump. The tendon of the left tibialis was freed, sectioned, and connected to a force displacement transducer. The resting tension was adjusted to 20 g. The sciatic nerve was stimulated by supramaximal 0.1-Hz stimuli of 0.2-msec duration through a bipolar electrode. Twitch tension was recorded on a polygraph. The muscle temperature was maintained at 37–38 C. Org NC 45 was administered intravenously by continuous infusion until 90% depression of twitch tension was obtained. When the infusion rate of Org NC 45 required to maintain a 90% depression of twitch tension remained constant for at least 15 minutes, neostigmine, pyridostigmine, or 4-aminopyridine, or a combination of these drugs was given as intravenous bolus. Time from antagonist administration to peak effect (onset), magnitude of antagonism, and time from antagonist administration to 50% return of the Org NC 45 depressed twitch tension (duration) were calculated. Only one dose of antagonist was studied in each rat. Initially, dose-response curves were determined for neostigmine, pyridostigmine, and 4-aminopyridine alone. Then neostigmine or pyridostigmine was combined with various doses of 4-aminopyridine to determine whether these drugs interact with each other in an additive or synergistic manner. The dose-response curves were compared by analysis of variance. These results were compared to those obtained earlier when pancuronium was used as the neuromuscular blocker.[5]

## Results

$ED_{50}$ (dose of antagonist which produced a 50% antagonism of the Org NC 45 depressed twitch tension) of neostigmine, pyridostigmine, and 4-aminopyridine were 14.5, 75, and 466 μg/kg, respectively (Figs. 1 to 3). The dose-response curves did not significantly deviate from parallelism. Extension of a

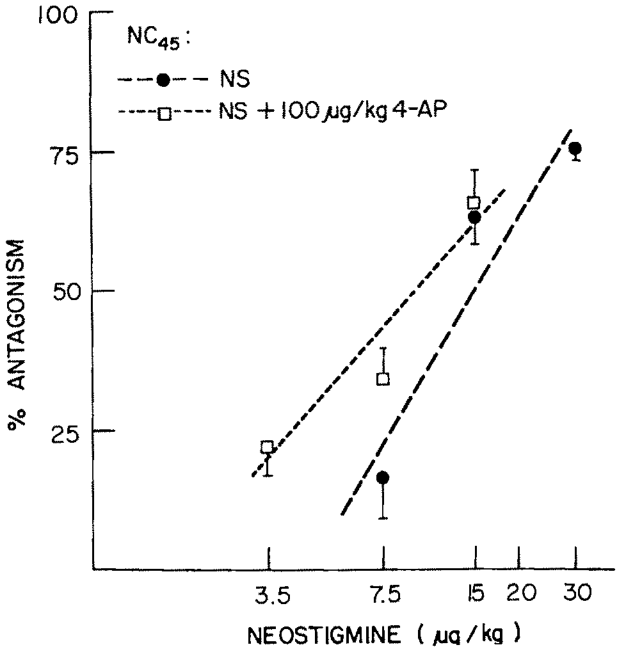


FIG 1. Effect of neostigmine (NS) alone and given with 4-aminopyridine (4-AP, 100 μg/kg) on percent antagonism of the Org NC 45 depressed twitch. Vertical lines represent the mean ± SE of six rats.

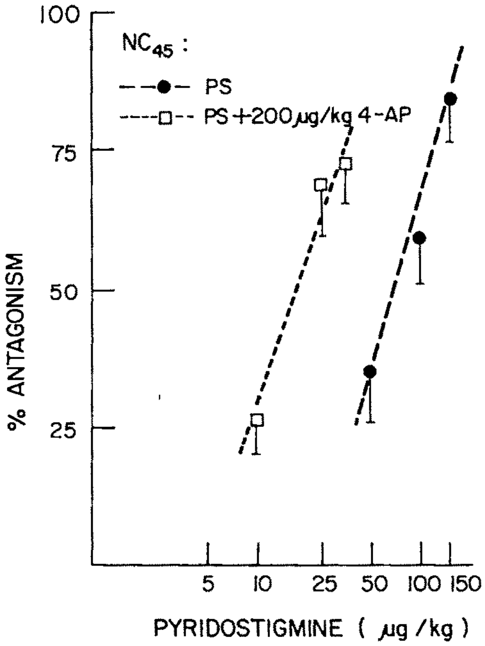


FIG 2. Effect of pyridostigmine (PS) alone and given with 4-aminopyridine (4-AP, 200 μg/kg) on percent antagonism of the Org NC 45 depressed twitch. Vertical lines represent the mean ± SE of six rats.

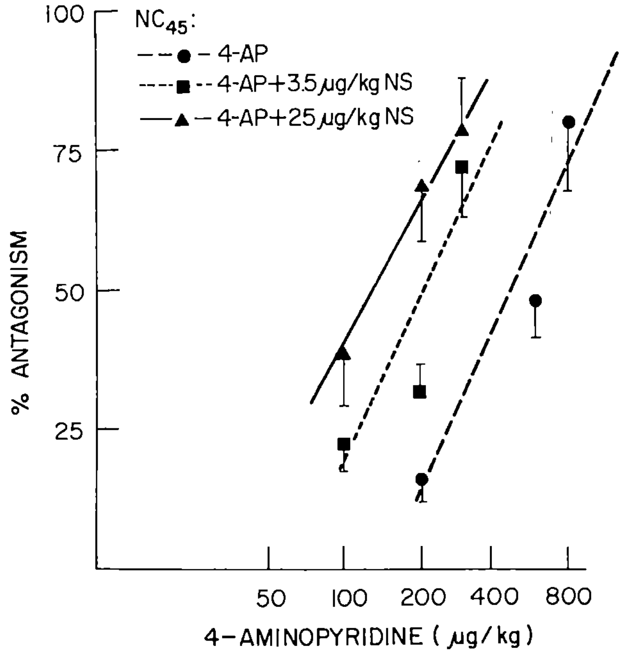


FIG 3. Effect of 4-aminopyridine alone and given with neostigmine (NS), 3.5 µg/kg, and pyridostigmine (PS), 25 µg/kg, on percent antagonism of the Org NC 45 depressed twitch. Vertical lines represent mean ± SE of six rats.

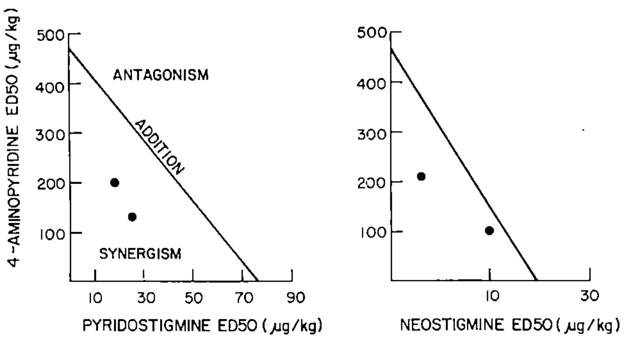


FIG 4. Correlation of the $ED_{50}$ (dose which produced a 50% antagonism of the Org NC 45 depressed twitch) of 4-aminopyridine, neostigmine, and pyridostigmine alone from which the line of identity was formed. Dots represent the $ED_{50}$ of various combinations of the above drugs.

linear regression line for 4-aminopyridine indicates that the 100-µg/kg dose should produce no antagonism (Fig 4); yet with this dose of 4-aminopyridine, the $ED_{50}$ of neostigmine was decreased from 14.5 to 9.8 µg/kg (Fig 1). With the addition of 200 µg/kg of 4-aminopyridine, which produced 14.8% antagonism by itself, the $ED_{50}$ of pyridostigmine was decreased from 75.1 to 17.5 µg/kg (Fig 2). The $ED_{50}$ of 4-aminopyridine was decreased from 466 µg/kg to 130 µg/kg and to 215 µg/kg by the addition of 25 µg/kg of pyridostigmine and 3.5 µg/kg of neostigmine, respectively, doses of pyridostigmine and neostigmine which by themselves caused no antagonism of the Org NC 45 depressed twitch. The $ED_{50}$ values of the various combinations of 4-aminopyridine plus neostigmine or pyridostigmine (Fig 3) were plotted against an isobologram constructed from the $ED_{50}$ values of the drugs alone. The combination of 4-aminopyridine with either neostigmine or pyridostigmine produced an effect greater than simple addition (Fig 4).

When equivalent levels of antagonism are compared, 4-aminopyridine increased the onset time but not the duration of action of neostigmine ($p < 0.05$) (Fig 5). In contrast, although 4-aminopyridine tended to lengthen the onset times of pyridostigmine, the differences were not significant (Fig 6). 4-Aminopyridine prolonged the duration of pyridostigmine action (Fig 6).

## Discussion

From the results of this study, we conclude that neostigmine, pyridostigmine, 4-aminopyridine, and their combinations are all effective antagonists of neuromuscular blockade produced by Org NC 45.

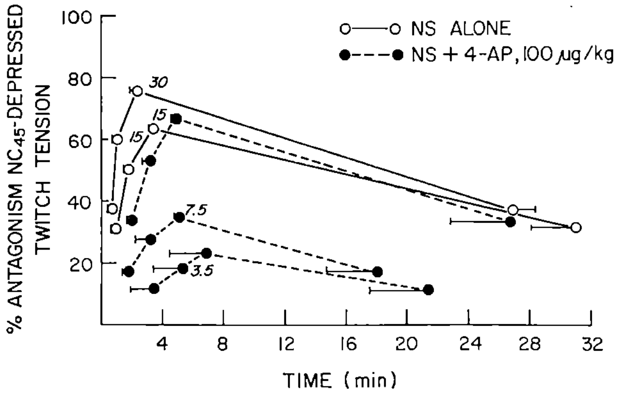


FIG 5. Correlation between time (minutes) and percent antagonism of Org NC 45 depressed twitch with neostigmine (NS) alone or with 4-aminopyridine (4-AP). Numbers beside drug abbreviations indicate doses.

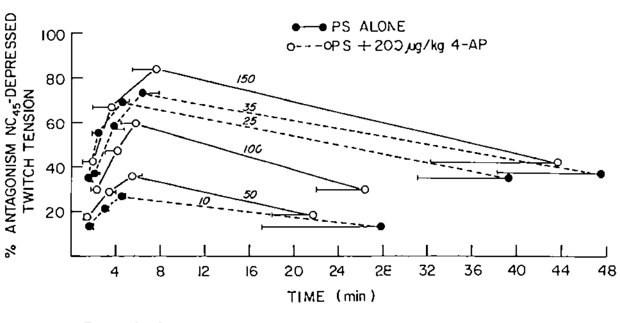


FIG 6. Correlation between time (minutes) and percent antagonism of Org NC 45 depressed twitch with pyridostigmine (PS) alone or with 4-aminopyridine (4-AP). Numbers beside drug abbreviations indicate doses.

**TABLE**

**Comparison of $ED_{50}$* of Neostigmine, Pyridostigmine, and 4-Aminopyridine Alone or in Combination Required to Antagonize an Org NC 45 or Pancuronium Neuromuscular Blockade**

| Antagonist | Org NC 45 | Pancuronium |
|---|---|---|
| | µg/kg | |
| Neostigmine (N) | 14.5 | 18 |
| Pyridostigmine (P) | 75 | 49 |
| 4-Aminopyridine (4-AP) | 466 | 440 |
| N + 4-AP, 100 µg/kg | 9.8 | 7.4 |
| P + 4-AP, 200 µg/kg | 18 | 11 |
| 4-AP + N, 3.5 µg/kg | 215 | 220 |
| 4-AP + P, 25 µg/kg | 130 | 76 |

* Dose of antagonist which produced a 50% antagonism of pancuronium or Org NC 45 depressed twitch.

Comparison of the $ED_{50}$ values from this study with those from an identical study performed previously with pancuronium[5] indicate no difference between Org NC 45 and pancuronium (Table). We, therefore, presume that the general clinical guidelines for antagonist administration for pancuronium probably also apply to Org NC 45. Clinical trials are required, however, to determine whether an anticholesterase-4-aminopyridine combination has any advantage over use of the drugs alone.[6]

The lack of cardiovascular changes and shorter duration of action of Org NC 45,[1] combined with equivalent antagonism when compared to d-tubocurarine and pancuronium, support the need for clinical trials with Org NC 45.

## REFERENCES

1. Booij, LHDJ, Edwards RP, Sohn YJ, et al: Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine, and *d*-tubocurarine in dogs. Anesth Analg 59:26–30, 1980
2. Stoyanov, E, Vulchev P, Shturbova M, et al: Clinical electromyomethanographic and electromyographic studies in decurarization with pyridine. Anaesthesiol Intensivmed 4:139–142, 1976
3. Booij LHDJ, Miller RD, Crul JF: Neostigmine and 4-aminopyridine antagonism of lincomycin-pancuronium neuromuscular blockade in man. Anesth Analg 57:316–321, 1978
4. Lee C, de Silva AJC: Interaction of neuromuscular blocking effects of neomycin and polymyxin B. Anesthesiology 50:218–220, 1979
5. Miller RD, Dennissen PAF, van der Pol F, et al: Potentiation of neostigmine and pyridostigmine by 4-aminopyridine in the rat. J Pharm Pharmacol 30:699–702, 1978
6. Miller RD, Booij LHDJ, Agoston S, et al: 4-Aminopyridine potentiates neostigmine and pyridostigmine in man. Anesthesiology 50:416–420, 1979

ANESTH ANALG
59:35-39, 1980

# Maternal Halothane Anesthesia Reduces Cerebral Blood Flow in the Acidotic Sheep Fetus

**Richard J. Palahniuk, MD,* George A. Doig, MD,† Garry N. Johnson, MD,‡ and Michael P. Pash, MD†**

PALAHNIUK, R. J., DOIG, G. A., JOHNSON, G. N., AND PASH, M. P.: Maternal halothane anesthesia reduces cerebral blood flow in the acidotic sheep fetus. Anesth Analg 59:35–39, 1980.

Cerebrovascular autoregulation is lost during fetal asphyxia as cerebral vessels undergo compensatory vasodilation. In such a situation, maternal anesthetics, which decrease fetal arterial blood pressure and cardiac output, may further aggravate cerebral hypoxia. To examine this possibility, we prepared six pregnant ewes in such a manner as to be able to measure fetal regional cerebral blood flow in utero during acidosis produced by partial umbilical cord compression both before and after 15 minutes of halothane anesthesia given to the mother.

Umbilical cord compression in the absence of anesthesia caused fetal metabolic and respiratory acidosis as evidenced by a decrease in arterial pH from 7.34 to 7.05; fetal arterial oxygen saturation simultaneously decreased from 29 to 17%. Halothane anesthesia administered to the mother of the acidotic fetus caused further aggravation of fetal acidosis (arterial pH 6.85) and oxygen desaturation (10%) and the fetus became markedly hypotensive.

Blood flow to four cerebral areas increased 27 to 69% above control levels in the fetus during acidosis in the absence of maternal anesthesia but decreased to levels 30 to 42% below acidosis values when maternal anesthesia was combined with fetal acidosis. These data suggest that potent cardiovascular depressant anesthetics administered to the mother in the presence of fetal acidosis could decrease fetal cerebral oxygen delivery by interfering with fetal cardiovascular compensation during acidosis and reducing fetal cerebral blood flow.

**Key Words:** ANESTHESIA, Obstetric; PREGNANCY: fetal blood flow; ANESTHETICS, Volatile: halothane.

PERINATAL asphyxia exposes the fetal brain to the risk of permanent damage.[1] In sheep[2] and probably also in humans,[3] the normal response to fetal asphyxia includes compensatory cerebrovascular dilation. Cerebral perfusion then becomes pressure dependent. Loss of normal cerebrovascular autoregulatory mechanisms in the asphyxiated fetus raises the possibility that factors including maternal general anesthesia, which may depress fetal (or neonatal) blood pressure or cardiac output, may reduce cerebral perfusion and thereby aggravate cerebral hypoxia.

Since the detection of fetal distress often leads to maternal anesthesia to promote rapid delivery of the fetus either vaginally or by cesarean section, we investigated the effects of a potent cardiovascular depressant anesthetic on fetal cerebrovascular responses to acidosis.

## Methods

This study was approved by our Animal Experimentation Committee as conforming to rigid guidelines for the humane use of animals in research. Six near-term pregnant ewes estimated to be at 130 to 140

---

* Professor.

† Research Fellow.

‡ Assistant Professor.

Supported by grants from the Manitoba Medical Services Foundation and the Medical Research Council of Canada.

Received from the Department of Anesthesia, University of Manitoba and Health Sciences Centre, Winnipeg, Manitoba, Canada R3E OZ3. Accepted for publication September 4, 1979. Presented in part at the International Anesthesia Research Society Meeting, March 1979, Hollywood, Florida.

Reprint requests to Dr. Palahniuk.

days of gestation (term = 150 days) were employed in the study. On the day prior to production of fetal asphyxia, the ewe was anesthetized with halothane and oxygen, endotracheally intubated, and ventilated to maintain normal arterial $P_{CO_2}$. The fetus was exposed through a hysterotomy incision and an axillary artery catheter was passed a measured distance into the common brachiocephalic trunk. A catheter was placed in the inferior vena cava via the femoral vein and a femoral artery catheter was inserted. An inflatable occlusion loop was placed around the umbilical cord. Maternal femoral artery and vein catheters were inserted. All catheters were brought to the skin in the ewe's flank and the incisions were closed.

Mother and fetus were allowed to recover for at least 20 hours following the preparatory surgery, and no study was performed unless maternal and fetal blood gases, acid-base balance, and blood pressure were near normal. During each study, maternal and fetal blood pressures and heart rates were monitored continuously via the femoral artery catheters using Statham P-23 transducers connected to a recording Beckman polygraph. Maternal and fetal arterial $P_{O_2}$, $P_{CO_2}$, and pH were measured on an Instrumentation Laboratories blood-gas analyzer and temperature corrected. Base excess and fetal oxygen saturation ($Sa_{O_2}$) were calculated using the appropriate nomograms.[4] Fetal regional cerebral blood flow (rCBF) measurements were made using 15-$\mu$ microspheres labeled with gamma-emitting $^{141}Ce$, $^{51}Cr$, or $^{85}Sr$. Spheres were injected into the inferior vena cava and achieved high concentrations in blood perfusing the brain by passing through the foramen ovale. The concentration of spheres present in blood perfusing the brain was determined by withdrawing blood at a fixed rate from the axillary artery catheter before, during, and after the injection. Blood flow to any region of the brain can be calculated using the equation:

$$\text{Blood flow (ml/100 g/min)} = Fa \times \frac{i\ \text{(brain sample)}}{i\ \text{(blood)}}$$

where $Fa$ = sampling rate of blood from the axillary artery over the period of microsphere injection; $i$ (brain sample) = counts per 100 grams of brain tissue; $i$ (blood) = counts in the axillary blood sample. This method of measuring regional cerebral blood flow has been validated by us[2] as well as other investigators.[5-7]

On the day of each study control measurements of rCBF, arterial blood gas tensions, and acid-base balance were made with the awake ewe standing quietly in her cage. Following this, the fetus was made acidotic to a pH near 7.05 by incremental inflation of the umbilical cord occlusion loop over 1 to 2 hours. After pH 7.05 had been achieved and remained stable for 30 minutes, measurements of rCBF, blood gas tensions, and acid-base balance were again made. The mother was then anesthetized with 4% halothane in oxygen by face-mask until she lost consciousness, at which time she was paralyzed with 60 mg of succinylcholine for insertion of an endotracheal tube following which anesthesia was maintained with 1% halothane in oxygen for 15 minutes. After 15 minutes of normocapneic maternal anesthesia, the final (acidosis + anesthesia) measurements of rCBF, arterial blood gas tensions, and acid-base balance were made.

Following completion of the study, mother and fetus were sacrificed and autopsies were performed to confirm proper placement of catheters. Fetal brain samples were obtained from cerebral cortex, cerebellum, brain stem, and basal ganglia. Gamma counts for each of the isotopes in the weighed tissue samples as well as the axillary blood samples were determined in a Searle gamma well-counter. Blood flows to each region of the brain at the three periods (control, acidosis, and acidosis-anesthesia) were then calculated as described previously.[2] Cerebral oxygen delivery during each period was calculated as rCBF × $Sa_{O_2}$. Although this value will not be an absolute value for oxygen delivery, we found that the fetal hemoglobin does not change more than ±5% in fetuses subjected to blood sampling so that this calculated value gives a close indication of oxygen delivery. Data were analyzed using the paired *t*-test and regression and correlation analysis as indicated. Means and standard errors for pH data were obtained by analyzing the pH values directly.

## Results

Maternal responses during the experimental periods are shown in Table 1. The degree of maternal cardiovascular depression suggests light to moderate anesthesia which we previously showed[8] to be associated with maintenance of uterine blood flow and fetal well-being in the normal sheep fetus in utero.

Fetal cardiovascular and acid-base responses are shown in Table 2. Halothane anesthesia in the mother was associated with deterioration in the condition of the fetus with the development of hypotension and a worsening of the blood gas tensions and acid-base balance. Corresponding fetal rCBF changes are shown

**TABLE 1**

**Maternal Data (Mean ± SE)**

| | Control | Acidosis | Acidosis-Anesthesia |
|---|---|---|---|
| Arterial blood pressure (torr) | 89.5 ± 5.2 | 87.0 ± 6.8 | 55.7* ± 5.8 |
| $Pa_{O_2}$ (torr) | 85.6 ± 5.4 | 87.3 ± 6.4 | 400.8* ± 50.4 |
| $Pa_{CO_2}$ (torr) | 29.7 ± 1.4 | 33.0 ± 6.1 | 36.2 ± 3.4 |
| pH | 7.51 ± 0.02 | 7.44 ± 0.06 | 7.44 ± 0.04 |

* Significantly changed from control and acidosis periods ($p < 0.05$).

**TABLE 2**

**Fetal Data (Mean ± SE)**

| | Control | Acidosis | Acidosis-Anesthesia |
|---|---|---|---|
| Arterial blood pressure (torr) | 54.8 ± 5.6 | 58.4 ± 7.8 | 35.3† ± 6.7 |
| $Pa_{O_2}$ (torr) | 15.3 ± 0.6 | 14.7 ± 1.0 | 15.4 ± 2.0 |
| $Pa_{CO_2}$ (torr) | 46.3 ± 2.0 | 70.6* ± 6.8 | 101.6† ± 14.7 |
| pH | 7.34 ± 0.04 | 7.05* ± 0.04 | 6.85† ± 0.05 |
| Base excess (meq/L) | 0.0 ± 2.4 | −7.1* ± 1.3 | −9.0* ± 0.9 |
| $Sa_{O_2}$ (%) | 28.8 ± 2.0 | 16.5* ± 3.6 | 9.8† ± 3.3 |

* Significantly changed from control period ($p < 0.05$).
† Significantly changed from control and acidosis perids ($p < 0.05$).

**TABLE 3**

**Fetal Regional Cerebral Blood Flow (Mean ± SE)**

| | Control | Acidosis | | Acidosis-Anesthesia | |
|---|---|---|---|---|---|
| | | Measurement | Change from control | Measurement | Change from acidosis |
| | *ml/100 g/min* | *ml/100 g/min* | % | *ml/100 g/min* | % |
| Cerebral cortex | 154 ± 23 | 212 ± 25 | +37 | 127† ± 45 | −40 |
| Cerebellum | 237 ± 23 | 300* ± 39 | +27 | 188† ± 63 | −37 |
| Basal ganglia | 204 ± 20 | 354* ± 35 | +68 | 204† ± 62 | −42 |
| Brain stem | 230 ± 30 | 389* ± 67 | +69 | 273 ± 97 | −30 |

* Significantly changed from control ($p < 0.05$).
† Significantly changed from acidosis ($p < 0.05$).

in Table 3. The acidotic period was associated with increases in cerebral flow ranging from 27 to 69%. After halothane anesthesia was administered to the mother rCBF levels in the acidotic fetus were 30 to 42% reduced.

The Figure relates changes in rCBF to changes to mean fetal arterial blood pressure during the acidosis-anesthesia period. The relationship between the change in rCBF and the change in mean arterial blood pressure approached significance in the basal ganglia (r = 0.758), cerebellum (r = 0.776), and the cerebral cortex (r = 0.70), ($p < 0.1$), but not in the brain stem (r = 0.629). There was no correlation of rCBF to changes in fetal pH, $Pa_{CO_2}$ or $Sa_{O_2}$.

Regional rates of cerebral oxygen delivery in the fetus during the acidosis and acidosis-anesthesia periods are summarized in Table 4. Marked reductions in oxygen delivery to all areas of the fetal brain were associated with maternal halothane anesthesia. Fetal blood loss during sampling averaged 24 ml for the entire study period. This represents about 7% of the blood volume of the average fetus.

## Discussion

Partial umbilical cord compression was chosen as the method to produce fetal acidosis because predictable levels of pH could be produced gradually without giving the mother drugs or anesthetics which might in themselves have affected fetal rCBF. We have been able to maintain stable fetal acidosis for several hours using carefully controlled umbilical cord compression in other studies in our laboratory.[2] Further fetal deterioration following the administration of halothane

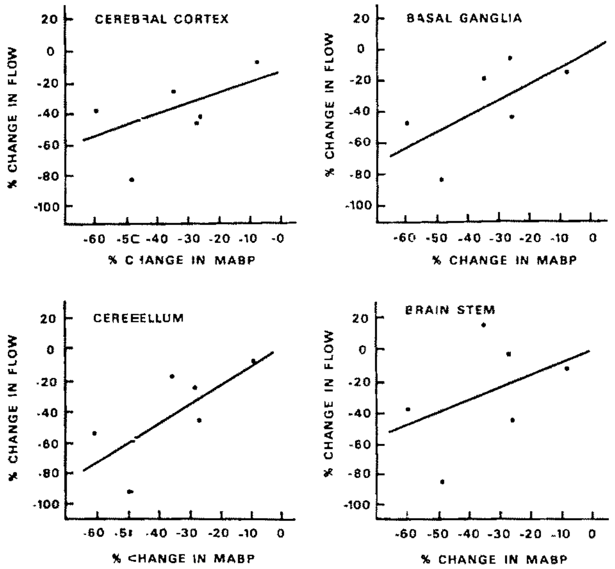


FIGURE. Changes in blood flow to four fetal cerebral regions as a function of changes in fetal mean arterial blood pressure (MABP) during fetal acidosis combined with maternal halothane anesthesia.

**TABLE 4**

**Fetal Cerebral Oxygen Delivery as Percent of Control (Mean ± SE)**

| | Acidosis | Acidosis-Anesthesia |
|---|---|---|
| Cerebral cortex | 77.8 ± 18.1 | 27.8* ± 11.8 |
| Cerebellum | 72.3 ± 21.5 | 27.4* ± 9.9 |
| Basal ganglia | 99.6 ± 20.4 | 33.5* ± 10.2 |
| Brain stem | 95.8 ± 21.4 | 41.0† ± 11.5 |

* Significantly changed from control ($p < 0.01$) and acidosis ($p < 0.05$).
† Significantly changed from control only ($p < 0.01$).

to the mother was abrupt and associated with the beginning of the anesthesia. The severe maternal metabolic changes produced during the anesthesia could have been responsible for the cardiovascular changes seen in the fetus, but the maternal halothane anesthesia was still directly or indirectly the cause of the changes observed.

Fetal responses to umbilical cord compression were similar to those seen in our previous studies.[2] Marked respiratory and metabolic acidosis occurred, along with reduction in oxygen saturation even though fetal $Pa_{O_2}$ was not reduced. The fetal $Pa_{O_2}$ in the control period was lower than usually seen in control animals although approaching values reported in some series[9] and in our other chronically prepared pregnant ewes. This could represent an effect of maternal anxiety as well.[10] It is difficult to explain why we failed to see a reduction in fetal $Pa_{O_2}$ with inflation of the occlusion loop sufficient to reduce fetal pH to 7.05. This finding has been consistent in our previous studies[2, 12] as well as those now in progress. Perhaps because we are sampling from the axillary artery above the ductus arteriosus we are seeing blood more representative of umbilical venous blood than mixed arterial, although we would expect a corresponding lower $Pa_{CO_2}$ if this were the explanation. The maintenance of the fetal $Pa_{O_2}$ with maternal anesthesia is easier to explain since maternal $Pa_{O_2}$ was raised to 401 and placental transfer of oxygen would be correspondingly greater. The shift in the oxyhemoglobin dissociation curve produced by the acidosis was primarily responsible for the reduction in oxygen saturation.

Because the near-term fetus maintains very active vascular reflexes,[11] the response to the acidotic insult was to increase cerebral blood flow by maximally dilating the cerebral vasculature. Previous studies in our laboratory[2] as well those by Lou et al,[3, 12] have suggested that the acidotic fetus and newborn have impaired cerebrovascular autoregulation. We found that elevations or reductions of blood pressure of 25% from normal in acidotic fetuses was associated with corresponding increases in CBF (work in progress) whereas the normal fetus appears to autoregulate its CBF.[13] The reductions in fetal blood pressure, cerebral blood flow, and cerebral oxygen delivery seen with maternal halothane anesthesia were thus not unexpected. Other drugs and anesthetics that have potent cardiovascular depressant effects might be expected to reduce similarly fetal blood pressure and rCBF during acidosis.

The greatest increase in blood flow during fetal acidosis in the absence of maternal anesthesia occurred in the brain stem and basal ganglia areas (+69% and +68%) with the least in cortical and cerebellar areas (+37% and +27%). This agrees with patterns of brain damage reported by other investigators[1] where slow partial asphyxia resulted in damage mainly to the cortical areas.

Interpretation of the present data and extrapolation to clinical situations are difficult. The fetuses we studied were severely acidotic (pH 7.05) before anesthesia was induced in the mother. Perhaps less severely compromised fetuses might be better able to tolerate depressant anesthetic agents. In addition, cerebral blood flow must be considered in relation to cerebral oxygen consumption. Some anesthetics, barbiturates, for example, may protect the brain from asphyxia, apparently by decreasing oxygen requirements more than oxygen supply.[14, 15] Although this type of protection has not been demonstrated for inhalation anesthetics, it is possible that they may reduce cerebral oxygen requirements as well as cerebral perfusion and thus partially protect the fetal brain from the effects of asphyxia. Until such evidence is obtained, however, we must carefully consider possible adverse fetal cardiovascular and cerebrovascular effects of the maternal inhalation anesthetic technique we choose when there is evidence of fetal asphyxia.

## REFERENCES

1. Myers RE: Two patterns of perinatal brain damage and their conditions of occurrence. Am J Obstet Gynecol 112:246–276, 1972
2. Johnson GN, Palahniuk RJ, Tweed WA, et al: Regional cerebral blood flow changes during severe fetal asphyxia produced by slow partial umbilical cord compression. Am J Obstet Gynecol 135:48–52, 1979
3. Lou HC, Lassen NA, Friis-Hansen B: Impaired autoregulation of cerebral blood flow in the distressed newborn infant. J Pediatr 92:118–121, 1979
4. Hellegers AE, Schrueffes JJA: Nomograms and empirical equations relating oxygen tension, percent saturation and pH in maternal and fetal blood. Am J Obstet Gynecol 81:377–384, 1961
5. Hales JRS: Radioactive microsphere techniques for studies of the circulation. Clin Exp Pharmacol Physiol (Suppl) 1:31–46, 1974
6. Roudolph AM, Heymann MA: The circulation of the fetus in utero: methods for studying the distribution of blood flow, cardiac output and organ flow. Circ Res 21:163–184, 1967
7. Marcus ML, Heistad DD, Erhardt JC, et al: Total and regional cerebral blood flow measurement with 7-10, 15, 25 and 50 $\mu$ microspheres. J Appl Physiol 40:501–507, 1976
8. Palahniuk RJ, Shnider SM: Maternal and fetal cardiovascular and acid-base changes during halothane and isoflurane anesthesia in the pregnant ewe. Anesthesiology 41:462–472, 1974
9. Wolkoff AS, Bawden JW, Flowers CE, et al: The effects of anesthesia on the unborn fetus. Am J Obstet Gynecol 93:311–320, 1965
10. Shinder SM, Wright RG, Levinson G, et al: Uterine blood flow

and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology 50:524–527, 1979

11. Dawes GS: Birth asphyxia, resuscitation and brain damage, in Foetal and Neonatal Physiology. Chicago, Year Book Medical Publishers, 1968, pp 141–159
12. Lou HC, Lassen NA, Tweed WA, et al: Pressure passive cerebral blood flow and breakdown of the blood-brain barrier in experimental fetal asphyxia. Acta Pediatr Scand 68:57–63, 1979
13. Purves JM, James IM: Observations on the control of cerebral blood flow in the sheep fetus and newborn lamb. Circ Res 25: 651–667, 1969
14. Steen PA, Michenfelder JD: Barbiturate protection in tolerant and non-tolerant hypoxic mice: comparison with hypothermic protection. Anesthesiology 50:404–408, 1979
15. Michenfelder JD, Theye RA: Cerebral protection by thiopental during hypoxia. Anesthesiology 39:510–517, 1973

---

## Autonomic Effect of Muscle Relaxants

The influence of gallamine, pancuronium, suxamethonium, and d-tubocurarine on adrenergic neurotransmission was studied in the isolated saphenous vein of the dog. Pancuronium but not the other muscle relaxants increased significantly the response to sympathetic stimulation and to exogenous norepinephrine; these increases were abolished after blockade of neuronal uptake by cocaine. Pancuronium and gallamine inhibited both the relaxation produced by lower doses of acetylcholine added during sympathetic stimulation (prejunctional effect) and the direct contractions evoked by high doses of the amine (postjunctional effect). In strips previously incubated with [$^3$H]-norepinephrine, gallamine had no effect on [$^3$H]norepinephrine efflux in basal conditions and during sympathetic stimulation; it increased markedly the efflux evoked by sympathetic stimulation in the presence of acetylcholine, confirming that gallamine inhibits the prejunctional effect of the latter on adrenergic transmission. When extrapolated to the intact organism, the present experiments indicate that gallamine and pancuronium augment the release of norepinephrine in vascular tissue under vagal control, which explains in part the cardiovascular effects of these muscle relaxants. *(Vercruysse P, Bossuyt P, Hanegreefs G: Gallamine and pancuronium inhibit pre- and postjunctional muscarinic receptors in canine saphenous veins. J Pharmacol Exp Ther 209:225–230, 1979)*

ANESTH ANALG
59:40-44, 1980

# Percutaneous Cervical Central Venous Line Placement: A Comparison of the Internal and External Jugular Vein Routes

**Kumar G. Belani, MB, BS,* Joseph J. Buckley, MD,† John R. Gordon, MD,‡ and Wifrido Castaneda, MD§**

BELANI, K. G., BUCKLEY, J. J., GORDON, J. R., AND CASTANEDA, W.: Percutaneous cervical central venous line placement: a comparison of the internal and external jugular vein routes. Anesth Analg 59:40–44, 1980.

To compare the rate of success and incidence of complications associated with two currently popular routes of percutaneous central venous cannulation, we studied 167 patients in whom either internal or external jugular vein catheterization was attempted. Internal jugular vein (IJV) catheterization (125 patients) was successful in 91%; an intrathoracic location was achieved in 100%; complications occurred in 12.8%. Complications included one case of catheter malposition, one case of tension pneumothorax, and 12 instances of inadvertent carotid artery puncture, one resulting in a paratracheal hematoma and phrenic nerve compression. The success rate of IJV cannulation was higher and carotid artery puncture less frequent when an 18-gauge thin-walled needle and a straight guide-wire were used than when IJV cannulation was performed by blind puncture with a larger over-the-needle catheter. Delayed vein perforation occurred twice. External jugular vein cannulation (42 patients), using a "J" wire technique, yielded a 76% success rate: 93.7% of catheter tips reached an intrathoracic location. No complications occurred. We conclude that IJV cannulation is a more reliable means of percutaneous central venous line placement but is associated with a significant incidence of complications which can be reduced if a technique employing a scout needle and guide-wire is used.

**Key Words:** VEINS, Jugular: cannulation; MONITORING: central venous pressure.

DURING the last decade, central venous pressure (CVP) measurement has become an important part of management in critical care medicine. The procedure requires that an intravenous catheter line be placed so that its tip lies in an intrathoracic "central vein," usually the innominate vein or the superior vena cava. These central veins can be reached percutaneously from several different sites, i.e., the antecubital veins or the cervical veins. Each approach has its merits and disadvantages. Several authors[1-7] have reported successful central cannulation via the internal jugular veins (IJV) but the procedure is not without risk and numerous complications have occurred.[1, 2, 6-11] In 1974, Blitt and associates[12] described an approach via the external jugular vein (EJV) using a "J"-tipped guide-wire to facilitate passage of the catheter into the intrathoracic venous system. We have prospectively studied 167 patients in whom "central lines" were placed to compare the usefulness, reliability, and hazards of these two popular techniques.

---

* Medical Fellow, Department of Anesthesiology.

† Professor and Interim Head, Department of Anesthesiology.

‡ Professor, Department of Anesthesiology.

§ Assistant Professor, Department of Radiology.

Received from the Departments of Anesthesiology and Radiology, University of Minnesota Health Sciences Center, Minneapolis, Minnesota 55455. Accepted for publication July 29, 1979.

Reprint requests to Dr. Belani.

## Subjects and Methods

From November 1, 1977, through April 30, 1978, all surgical patients in whom a percutaneous cervical CVP line was placed for fluid management during anesthesia were subjects of the study. The procedure was performed by staff anesthesiologists, senior residents, or experienced nurse anesthetists. Either the EJV or IJV route was chosen by the anesthetist managing the patient. The decision usually depended upon whether the EJV was visible and the personal preference of the anesthetist. The procedure was performed using an aseptic technique with either local or general anesthesia and with the patient in a supine 30° Trendelenburg position. For IJV cannulation the right side was chosen in preference to the left and one of two techniques was used. In the first, the vein was entered directly with a 14-cm, 14- or 15-gauge Teflon over-the-needle catheter; the catheter was then advanced until a central location of its tip could be assumed. In the second technique, the Seldinger method[13] was applied: the IJV was punctured with a short (4 cm) 18-gauge thin-walled "guide" needle; a 35-cm, 0.089-cm outside diameter, flexible guide-wire was then passed through the needle, after which the needle was removed. A 14-cm, 14-gauge Teflon over-the-needle catheter was then advanced over the wire into the vein and the catheter was passed centrally. In both techniques, the topographic landmarks used were those described by Civetta et al[3]; the point of entry was 5 cm above the clavicle and 1 cm medial to the lateral edge of the sternocleidomastoid muscle with the needle angled 30° to the coronal plane and inserted along a path parallel to the anterior border of the sternocleidomastoid muscle. If inadvertent arterial puncture occurred with either technique, the needle was removed and pressure was applied over the puncture site; the cannulation was reattempted after 5 minutes. The procedure was abandoned if arterial puncture occurred again or if the vein could not be located in three attempts. An attempt was defined as inability to enter or cannulate the IJV after careful needle insertions and withdrawal. Successful central catheter placement was assumed when there was easy passage of the catheter and when aspiration yielded free return of venous blood.

For EJV cannulation, the technique described by Blitt et al[12] was used with slight modification. Percutaneous EJV puncture was performed with the same 18-gauge thin-walled needle described in the IJV technique but this time a "J"-tipped, 35-cm, 0.089-cm outside diameter, flexible guide wire was passed through the needle into the EJV. With the wire in the EJV the needle was removed and a 14-cm, 14- or 16-gauge Teflon catheter was passed over the wire into the vein. The wire was manipulated past venous bifurcations until a central position could be assumed and the catheter was then advanced over the wire to the central position. Failure of placement occurred when it was not possible to advance the J-wire beyond the clavicle. In this event the procedure was abandoned. In the technique described by Blitt venipuncture is performed directly with a long over-the-needle catheter through which the J-wire is then advanced.

In both IJV and EJV methods, evidence of successful intrathoracic placement was checked by obtaining free return of venous blood upon lowering the intravenous fluid reservoir and by noting fluctuation of a manometric fluid column with respirations. The catheters were taped securely and the puncture sites covered with an antibiotic ointment and a sterile occlusive dressing. A postoperative or postinsertion chest x-ray was taken in every case to verify the position of the tip of the catheter. Patients were examined daily for possible complications until the catheter was removed.

X-ray confirmation of catheter tip location provided the means to identify catheters that reached an intrathoracic (central) position versus those that took an aberrant course after apparent successful intrathoracic placement at the time of insertion. Catheter tips placed extrathoracically or those that terminated in tributaries draining into the large veins were considered malpositioned catheters.

The chi square test was used to determine statistical significance of differences in results. Comparison was made between the number of apparently successfully placed catheters in the internal and external jugular vein groups and the number attempted in each group. Similar comparisons between the two groups were made with respect to the number of catheter tips actually placed intrathoracically, and the number of complications that ensued. A comparison was also made in the IJV group between the number of catheters placed successfully with and without use of the "guide" needle and also between the number of times the carotid artery was punctured and the number of successful attempts. A $p$ value of $<0.05$ was considered significant.

All patients included in the study were to have a cervical central venous line placed as a matter of routine for surgical management (cardiovascular or massive abdominal or thoracic surgery). The decision to use the external or internal jugular vein was entirely that of the anesthetist managing the patient, and competence with or preference for one technique over the other was not controlled or considered in patient selection. Since the study was simply an analysis of procedures that were applied without respect to this investigation, approval of the Committee on Human Experimentation was not obtained.

## Results

The results of the study are summarized in Tables 1 and 2. Internal jugular vein cannulation was accomplished successfully in 91% of patients. All catheter tips reached an intrathoracic position. Of three catheterizations done via the left IJV, one tip was malpositioned in the left superior intercostal vein. Among the 125 attempts at cannulations, one resulted in tension pneumothorax and there were 12 instances of carotid artery puncture. The pneumothorax required tube thoracotomy. In one patient, puncture of the carotid artery resulted in a right paratracheal hematoma and phrenic nerve irritation, manifested by intermittent hiccups for 8 days which ceased when the hematoma resolved. No significant complications were noted in the other patients in whom the carotid artery was inadvertently punctured. Two serious delayed complications occurred following IJV cannulation. In one patient, an acute unilateral hydrothorax requiring chest tube draining occurred 48 hours after a catheter was successfully placed via the right IJV. In another patient, a unilateral pulmonary infiltrate suddenly appeared 7 days after a catheter was placed via the left IJV in the left superior intercostal vein. Both patients experienced acute dyspnea with hypoxemia, and blood could not be aspirated from the catheters. As soon as the diagnosis was confirmed by chest x-ray, the catheters were removed. The patients recovered completely.

External jugular vein catheterization was successful in 76% of patients; 94% of the catheter tips reached an intrathoracic location. Six catheter tips (14.3%) were directed away from the heart: four reached the contralateral innominate vein, one entered the ipsilateral IJV, and one entered an axillary vein. There were no complications, immediate or late, after EJV line placement.

## Discussion

This prospective study compares two popular percutaneous cervical routes for CV line placement. External jugular vein catheterizations produced no complications. This confirms the experience with this approach reported by Blitt et al.[12] However, our findings differ in some respects from those reported by Blitt, et al (Table 3). Our youngest patient was 3 years old, while the youngest in Blitt's series was 9 years old; furthermore, we cannulated five patients by the EJV route who were less than 10 years of age (3, 3½, 4, 8, and 9 years); cannulation was successful in all of these patients, probably because a shorter, finer needle was used to enter the EJV. On the other hand, our overall cannulation and intrathoracic placement success rate was lower than Blitt's. Although the reasons for these differences are not clear, the higher failure we observed may have been due to less vigorous attempts to twist the J-wire past vein junction obstructions or to a purely chance encounter with a

**TABLE 2**

**Catheter Tip Positions Obtained with Jugular Vein Cannulations**

| | Internal Jugular Vein | | External Jugular Vein | |
|---|---|---|---|---|
| | Right | Left | Right | Left |
| Right atrium | 10 | | 3 | |
| Superior vena cava | 98 | 2 | 18 | |
| Innominate vein | | | | |
| Ipsilateral | 3 | | 1 | 4 |
| Contralateral | | | 4 | |
| Other veins | | | | |
| Ipsilateral internal jugular vein | | | 1 | |
| Ipsilateral axillary vein | | | 1 | |
| Left superior intercostal vein | | 1 | | |
| Total | 111 | 3 | 28 | 4 |

**TABLE 1**

**Results of Jugular Vein Cannulations**

| Vein | No. attempted | Successful | | Intrathoracic catheter tips | | Malpositioned tips | | Complications | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % | No. | % |
| IJV | 125 | 114 | 91 | 114 | 100 | 1 | 0.8 | 16 | 13 |
| EJV | 42 | 32* | 76.2 | 30* | 93.7 | 2 | 6.3 | 0* | 0 |

* $p < 0.05$.

**TABLE 3**

**Comparison of Results of External Jugular Vein Catheterization in Study by Blitt et al[12] and This Study**

| | Blitt et al (1974) | Belani et al (1979) |
|---|---|---|
| Age group | 9–86 yr | 3–86 yr |
| Success rate | 96% | 76% |
| Intrathoracic success rate | 100% | 94% |
| Location of catheter tip: | | |
| Right atrium | 16.6% | 9.4% |
| Superior vena cava | 76% | 56.3% |
| Innominate vein | 7.3% | 28.1% |
| Other vein | 0 | 6.3% |
| Complications | Nil | Nil |

**TABLE 4**

**Relation between Success Rate, Carotid Artery Puncture, and Use of "Guide" Needle in 125 Internal Jugular Vein Cannulations**

| "Guide" needle used | No. attempted | Successful cannulations | | Carotid artery punctures | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Yes | 77 | 74 | 96.1 | 4 | 5.2 |
| No | 48 | 40* | 83.3 | 8* | 16.6 |
| Total | 125 | 114 | 91.0 | 12 | 9.6 |

* $p < 0.05$.

plexus termination of the EJV in some patients, as commented upon by Blitt et al.[12] Possible differences in the experience and skill of the anesthetists who performed the procedure could also have contributed to the lower success rate. The lower rate of placement of catheter tips in the right atrium could be related to our preference for a higher level of puncture or to the length of the necks of patients; longer catheters would obviate such proximal terminations. Six catheters passed away from the heart and two tips became malpositioned in extrathoracic veins. Such catheter malpositioning following percutaneous EJV cannulation has not been previously reported.

Our results with IJV cannulation also differ from those reported by others. In a recent study,[6] both rate of failure and rate of inadvertent puncture of the carotid artery were 20%. The two techniques employed in our study yielded statistically significant differences in success rates and incidence of puncture of the carotid artery (Table 4). When the short (guide) needle was used to puncture the IJV, the rate of successful cannulation was higher and the frequency of puncture of the carotid artery was only one third of the rate when direct puncture of the IJV with a long, large-bore, over-the-needle catheter was employed. Civetta et al[3] and Prince et al[6] previously recommended localization of the IJV with a fine needle, followed by final puncture with a large needle for catheter introduction. That method, although useful, is unnecessary if the Seldinger technique[13] is applied, and the need to repuncture the vein is obviated.

In the patients who developed tension pneumothorax and paratracheal hematoma, the IJV was entered directly with the long, over-the-needle catheter. Both complications could have been avoided if the fine needle and Seldinger technique[13] had been used. The severe hiccups that accompanied the right paratracheal hematoma was due to irritation of the right phrenic nerve; this type of isolated phrenic nerve injury has not been reported before. The two delayed complications (hydrothorax and pulmonary infiltrate) were also unusual. We believe they were caused by late penetration of the vein wall by the catheter tip. Carvell and Pearce[11] reported a similar complication and summarized previous occurrences, but in only one instance was a Teflon catheter implicated. Similar vein wall perforation could occur with an EJV catheter but is less likely because, as pointed out by Benotti et al,[5] an IJV catheter is more susceptible to motion within the vein, which enhances the potential for vein penetration.

Malpositioning and loop formation of IJV catheters, although rare, can occur.[14] Recently Krausz et al[15] reported aberrant termination of a left IJV catheter in the left superior intercostal vein. They postulated that an enlarged left superior intercostal vein secondary to portal hypertension may have fostered the aberrant termination. Our patient did not have portal hypertension or cirrhosis, and the left side was chosen only because there was a septic fistula on the right side of the neck.

Thus, comparing the two routes of cannulation (Table 1), there are statistically significant differences in the results obtained. The EJV route appears to be safer, but has a lower predictability for successful cannulation and results in a higher incidence of catheter malpositioning. On the other hand, the IJV method, although predictable and more reliable in providing access to the central veins, carries a greater risk of complication. This is perhaps understandable because the IJV is deeper and more closely related to structures that may be inadvertently damaged during cannulation. The use of a short fine needle and a straight guide-wire reduces the risk of puncture of the carotid artery and increases the success rate of IJV catheterization. Late vein wall perforation by the catheter tip can occasionally produce delayed complications.

## REFERENCES

1. English ICW, Frew RM, Pigott JPG, et al: Percutaneous cannulation of the internal jugular vein. *Thorax* 24:496–497, 1969
2. Jernigan WR, Gardner WC, Mahr MM, et al: Use of the internal jugular vein for placement of central venous catheter. *Surg Gynecol Obstet* 130:520–524, 1970
3. Civetta JM, Gabel JC, Gemer M: Internal jugular puncture with a margin of safety. *Anesthesiology* 36:622–623, 1972
4. Petty C: Alternate method of internal jugular venipuncture for monitoring central venous pressure. *Anesth Analg* 54:157, 1975
5. Benotti PN, Bothe A, Miller JDB, et al: Safe cannulation of the internal jugular vein for long term hyperalimentation. *Surg Gynecol Obstet* 144:574–576, 1977
6. Prince SR, Sullivan RL, Hackel A: Percutaneous catheterization of the internal jugular vein in infants and children. *Anesthesiology* 44:170–174, 1976
7. Rao TLK, Wong AY, Salem MR: A new approach to percutaneous catheterization of the internal jugular vein. *Anesthesiology* 46:362–364, 1977
8. Wisheart JD, Hassan MA, Jackson JW: A complication of percutaneous cannulation of the IJV. *Thorax* 27:496–499, 1972
9. Defalque RJ: Percutaneous catheterization of the internal jugular vein. *Anesth Analg* 53:116–121, 1974
10. Briscoe CE, Bushman JA, McDonald WI: Extensive neurological damage after cannulation of IJV. *Br Med J* 1:314, 1974
11. Carvell JE, Pearce DJ: Bilateral hydrothorax following internal jugular catheterization. *Br J Surg* 63:381–383, 1876
12. Blitt CD, Wright WA, Petty WC, et al: Central venous catheterization via the external jugular vein: a technique employing the J wire. *JAMA* 229:817–818, 1974
13. Seldinger SI: Catheter replacement of the needle in percutaneous arteriography: A new technique. *Acta Radiol* (*Stockh*) 39:368–376, 1953
14. Malatinsky J, Kadlic T, Majek M, et al: Misplacement and loop formation of central venous catheters. *Acta Anaesthesiol Scand* 20:237–247, 1976
15. Krausz MM, Berlatzky J, Eimerl D, et al: Aberrant position of a central venous catheter: a cause for inadequate fluid replacement in septic shock. *Crit Care Med* 6:337–338, 1978

---

## Hemodynamic Effects of the Trendelenburg Position

The effect of the Trendelenburg position (15 to 20 degree head-down tilt) on systemic and pulmonary hemodynamics in critically ill patients was examined in 61 normotensive and 15 hypotensive patients with acute cardiac illness or sepsis. In normotensive patients, the head-down tilt increased the preload of both right and left ventricles, increased cardiac output slightly, decreased systemic vascular resistance, and did not change the mean arterial pressure. This effect was probably mediated by baroreceptor stimulation. In hypotensive patients, the Trendelenburg position did not increase preload, slightly increased afterload, and decreased cardiac output. This study failed to document any beneficial hemodynamic effect of the Trendelenburg position in critically ill normotensive or hypotensive patients. *(Sibbald WJ, Paterson NAM, Holliday RL, et al: The Trendelenburg position: hemodynamic effects in hypotensive and normotensive patients. Crit Care Med 7:218–224, 1979)*

ANESTH ANALG
59:45-49, 1980

# Ketamine Acts on the Peripheral Sympathetic Nervous System of Guinea Pigs

**M. S. Juang, MD,* K. Yonemura, MD,* T. Morioka, MD,† and I. Tanaka, MD***

JUANG, M. S., YONEMURA, K., MORIOKA, T., AND TANAKA, I.: Ketamine acts on the peripheral sympathetic nervous system of guinea pigs. Anesth Analg 59:45–49, 1980.

The effects of ketamine on the peripheral sympathetic nervous system were studied in vitro by observing the amplitude of the nerve-mediated contraction of the vasa deferentia isolated from guinea pigs. Ketamine dissolved in the perfusate of an organ bath was applied to the tissues for 30 minutes and then washed out with a perfusate lacking ketamine for 90 minutes.

Ketamine in concentrations of $10^{-8}$ and $10^{-7}$ g/ml had no effect on contraction induced by hypogastric nerve (preganglionic) stimulation. At $10^{-6}$ g/ml, the drug had no significant effect during application but was associated with increased contractions during washout. At $10^{-5}$ and $10^{-4}$ g/ml, the drug showed a dose-related depression during application and an increase in contractions during washout after a $10^{-5}$ g/ml. Ketamine, $10^{-5}$ g/ml, increased contraction following transmural (postganglionic) stimulation and had a depressant effect at a concentration of $10^{-4}$ g/ml. It is concluded (1) that ketamine has dual effects on the nerve-mediated contraction of the vasa deferentia and (2) that cardiovascular responses to ketamine include peripheral effects of ketamine on sympathetic ganglia.

**Key Words:** ANESTHETICS, Intravenous: ketamine; SYMPATHETIC NERVOUS SYSTEM, ketamine.

EARLY pharmacologic studies in man and animals showed that ketamine produces cardiovascular stimulation and other autonomic excitatory reactions.[1-4] Later, the possible sites of the cardiovascular effects of ketamine were investigated by several workers. Although the role of baroreceptors in producing the cardiovascular responses to ketamine is inconclusive,[5,6] a number of reports[7-12] indicate that the cardiovascular responses to ketamine are centrally mediated. Ketamine, for example, does not produce a pressor response in dogs when activity of the peripheral sympathetic nervous system is blocked by epidural anesthesia.[7]

Previous studies have not excluded the possibility that ketamine may modify impulse propagation and/or transmission within the peripheral sympathetic nervous system. In fact, Nedergaard,[13] Montel et al,[14] and Hill et al[15] have shown an inhibitory effect of ketamine on the neuronal reuptake of norepinephrine, and Gallagher et al[11] have reported a depolarizing effect of ketamine on frog sympathetic ganglion cells. Clanachan and McGrath[12] have suggested that ketamine may have both inhibitory and excitatory effects on the sympathetic nervous system of rats, the former including inhibitory effects on the responses of the anococcygeus (smooth) muscles to nerve stimulation and the latter including small potentiating effects on the responses of the muscles to norepinephrine. The optimal doses for each effect were similar, the net effect being predominantly depression of the rat peripheral autonomic nervous system.

The present experiments were designed to examine the direct action of ketamine on the nerve-mediated contractions of the isolated smooth muscle prepara-

---

* Department of Physiology.

† Department of Anesthesiology.

Received from the Departments of Physiology and Anesthesiology, Kumamoto University Medical School, Honjo 2-2-1, Kumamoto, Japan. Accepted for publication July 28, 1979.

Reprint requests to Professor T. Morioka.

tions using a wide range of concentrations and thus to elucidate possible effects of ketamine on the peripheral sympathetic nervous system. Vas deferens preparations from guinea pigs[16] were used in which readily quantifiable contractions could be produced by either hypogastric nerve (preganglionic) or transmural nerve (postganglionic) stimulation.[17, 18]

## Methods

Guinea pigs (weighing 160 to 240 g) were stunned by a blow on the head and bled to death. Two preparations fixed in an organ bath as previously described in detail by Huković[16] were used (Fig 1).

### Isolated Hypogastric Nerve-Vas Deferens Preparation

In this preparation, the hypogastric nerve was passed through two platinum ring electrodes 2 to 3 mm apart ($S_1$ of Fig 1) and fixed with a pin. Electrical stimulation through the electrodes (hypogastric nerve stimulation) in such a preparation initiates impulses in the preganglionic nerve fibers which travel via the sympathetic ganglia to produce contractions of the vas deferens.[17, 18]

### Isolated Vas Deferens Preparation

In this preparation, the mesenteric investment overlaying the vas deferens was removed and the bladder end of the vas passed through two platinum ring electrodes 3 to 4 mm apart ($S_2$ of Fig 1) and fixed with a pin. Electrical stimulation through electrodes placed in this manner (transmural stimulation) initiates impulses in postganglionic nerve fibers which are located in the wall of the vas and which run in bundles parallel to the longitudinal axis of the vas thereby producing contraction of the vas.[17, 18]

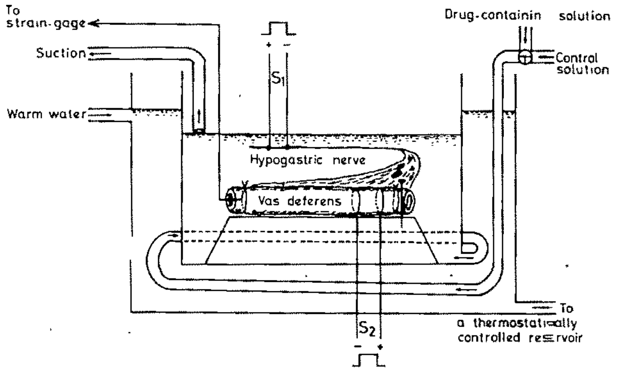


FIG 1. Schematic representation of the isolated hypogastric nerve-vas deferens preparation of the guinea pig and the perfusion system used in the experiment. Warm water from a thermostatically controlled reservoir was circulated through the jacket to maintain temperature of the perfusate at 34–36° C. Fresh Krebs solution constantly run through the polyethylene tube could be changed by turning a three-way stopcock to the perfusate containing the drug. Dots in the mesenteric investment above the vas deferens represent peripheral sympathetic ganglia of the hypogastric nerve.

Both preparations were immersed in an organ bath which was maintained at 34–36 C (Fig 1) and perfused continuously at a rate of 150 to 200 ml/hr with a Krebs solution of the following composition (in mM): NaCl 120; KCl 5.0; $CaCl_2$ 2.5; $MgSO_4$ 1.0; $NaHCO_3$ 25; $NaH_2PO_4$ 1.0; and glucose 11. The solution was equilibrated with a gas mixture of 95% $O_2$ and 5% $CO_2$, and had a pH of 7.4.

For the semi-isotonic recording of vas deferens contractions in response to stimulation of the hypogastric nerve or transmural stimulation, the testis end of the vas was connected to a force-displacement transducer (RP-2, Nihon Koden). Tetanic stimulation consisting of a train of pulses (30 Hz, 0.1 to 0.5 msec, pulse width) lasting 1 second were delivered through the platinum electrodes at 5-minute intervals in each experiment. The intensity of the stimuli was fixed for each preparation prior to drug application so as to produce a contraction up to two thirds of the maximum.

Ketamine hydrochloride (Sankyo Co, Ltd, Tokyo) was added to the perfusate in the desired concentration before each experiment. After application of ketamine for 30 minutes the tissue was rinsed by changing the perfusate back to a fresh Krebs solution lacking ketamine.

In the control experiment, Krebs solution was used as the perfusate throughout the period of observation. During the control study, the amplitude of vas deferens contractions in response to both hypogastric nerve stimulation and transmural stimulation diminished gradually as time passed. As shown in Figs 2 and 3, the mean amplitudes decreased with some fluctuations at a rate of 11 ± 2% (mean ± SEM, n = 10)/hr in the hypogastric nerve stimulation and 8 ± 1% (n = 10)/hr in the transmural stimulation. Therefore, data obtained during and after application of ketamine were compared with those data obtained at each corresponding time in the control experiments. Student's $t$ test was used to determine statistical significance of observed changes; $p < 0.05$ was taken as the minimal level of significance.

## Results

Ketamine at concentrations of $10^{-8}$ to $10^{-4}$ g/ml did not produce spontaneous contractions of the vas def-

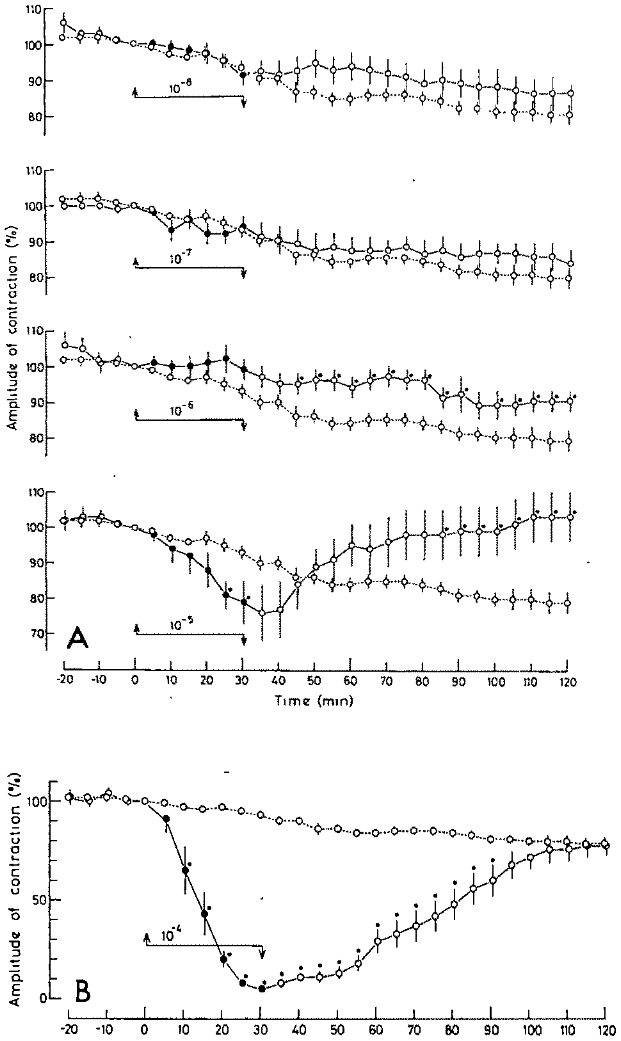


FIG 2. A, Effects of ketamine ($10^{-8}$ to $10^{-5}$ g/ml) on the amplitude of contractions of vas deferens induced by hypogastric nerve stimulation. Control experiment (O- - -O). Ketamine application for 30 minutes (●——●). Amplitudes are expressed as the percentage of the values obtained immediately before changing the perfusate to the test solution in each experiment (indicated by upward arrows). Open and solid circles represent the means of 10 experiments at each concentration with SEM; small black dots indicate statistically significant differences from the corresponding control values ($p < 0.05$). B, Same as A but with ketamine applied at a concentration of $10^{-4}$ g/ml.

erens in vitro but increased or decreased nerve-mediated contractions as described below.

### Effects of Ketamine on Amplitude of Vas Deferens Contractions Induced by Hypogastric Nerve Stimulation

The sequential changes in the amplitude of smooth muscle contractions induced by hypogastric nerve stimulation before, during, and after the application of ketamine at each concentration ($10^{-8}$ to $10^{-4}$ g/ml) are illustrated in Fig 2 along with data obtained in the control experiments.

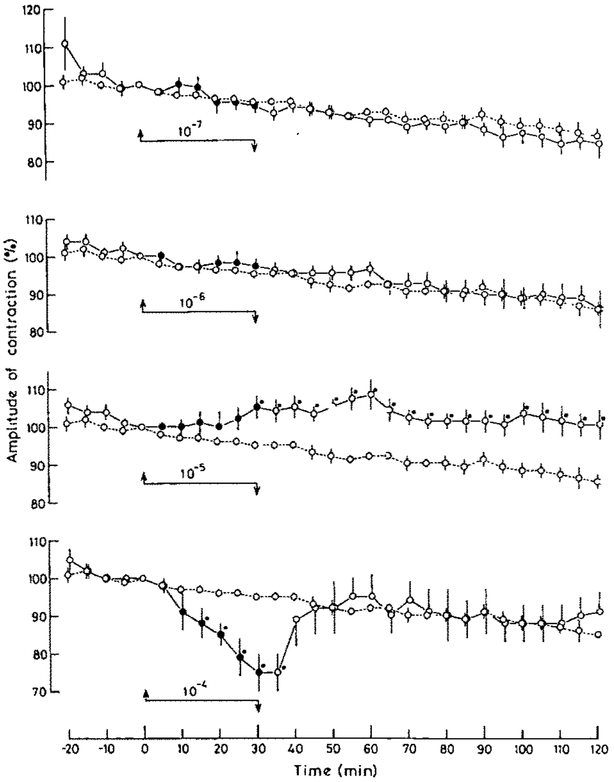


FIG 3. Effects of ketamine ($10^{-7}$ to $10^{-4}$ g/ml) on the amplitude of contractions of vas deferens induced by transmural stimulation. Definition of symbols is the same as in Fig. 2.

At concentrations of $10^{-8}$ and $10^{-7}$ g/ml, ketamine produced no significant change in the amplitude of contractions. During application of $10^{-6}$ g/ml for 30 minutes, in three of 10 preparations slight increases in amplitude (111 to 127% of the controls) occurred that were not statistically significant. However, during washout of ketamine, a slight but statistically significant increase in mean values was observed reaching 113% of control levels. Increasing the concentration of ketamine to $10^{-5}$ g/ml caused contractions to be depressed to 85% of control levels 30 minutes after application. However, the amplitude increased significantly as the tissues were washed with the ketamine-free perfusate for more than 55 minutes, reaching 131% of the controls within 90 minutes. At the highest concentration of ketamine, $10^{-4}$ g/ml (Fig 2B), contractions were almost completely inhibited to 5% of control levels after 30 minutes and returned to control levels 65 minutes after washout. In four cases in which $10^{-4}$ g/ml ketamine was applied and then washed out for more than 120 minutes, the mean amplitude increased to 142% of control.

### Effects of Ketamine on the Amplitude of Vas Deferens Contractions Induced by Transmural Stimulation

Fig 3 illustrates the sequential changes in the amplitudes of smooth muscle contractions induced by transmural stimulation before, during, and after the application of ketamine at concentrations of $10^{-7}$ to $10^{-4}$ g/ml, along with data obtained in control experiments.

At concentrations of $10^{-7}$ and $10^{-6}$ g/ml there were no significant changes in the contractions. At $10^{-5}$ g/ml, ketamine produced a slight but significant increase in the amplitude of contraction, reaching 110% of the control levels 30 minutes after application. This increase persisted during washout. On the other hand, at the highest concentration, $10^{-4}$ g/ml, ketamine produced significant depression of contractions to 78% of the control values 30 minutes after application. The depressed contractions recovered fairly rapidly to the control levels (within 15 minutes after the start of washout). During the washout period, contractions increased to 117 to 155% of the control levels in five of 10 instances, an increase that was, however, not statistically significant, probably due to a large variability in response.

## Discussion

Corssen and Domino[2] showed in their initial pharmacologic study that in man ketamine produces an anesthetic state with doses of 1.0 to 2.0 mg/kg of body weight. Even if the drug were given intravenously and if all remained in the circulating blood, these doses would result in plasma concentrations that would not exceed approximately $10^{-5}$ g/ml. Concentrations in the extracellular fluid where the drug exerts its pharmacologic action would be appreciably lower. For these reasons, and considering normal biologic variations, concentrations of $10^{-4}$ to $10^{-8}$ g/ml of ketamine were used in the present study.

At these concentrations, ketamine failed to produce spontaneous contraction of the guinea pig vas deferens in vitro but did produce changes in sympathetic nerve-mediated contractions. This indicates that the drug does not produce ganglionic or nerve-ending stimulation, as suggested by Traber and Wilson,[7] but that it probably modulates propagation or transmission of impulses within the peripheral sympathetic nervous system.

Ketamine produced in the present experiments depression of the nerve-mediated contractions when applied at relatively high concentrations. The contractions in response to the hypogastric nerve (preganglionic) stimulation were more effectively depressed than those in response to the transmural nerve (postganglionic) stimulation. These observations are consistent with the findings of Clanachan and McGrath[12] in the anococcygeus (smooth) muscle of pithed rats. This effect could be due to one or more of the following: (1) initiation and propagation of impulses were more effectively abolished in preganglionic than in postganglionic fibers; (2) release of or response to synaptic transmitter substances were more effectively inhibited in sympathetic ganglia than at sympathetic neuromuscular junctions; or (3) excitability of cell membranes was more effectively lowered in the sympathetic ganglion cells than in the smooth muscle fibers. The first explanation seems unlikely; such a local anesthetic-like action of ketamine would be more effective on postganglionic C-fibers than on the preganglionic B-fibers, as observed in frog sympathetic nerve fibers.[11] The second possibility is supported by the observation that ketamine decreases acetylcholine release from the motor nerve endings in rats[19] but decreases postsynaptic membrane sensitivity to acetylcholine in both frog sympathetic ganglia[11] and in rat uterus smooth muscle[20] while potentiating smooth muscle response to norepinephrine in rats when applied at high concentrations.[12] There is no experimental evidence to support the third possibility.

Ketamine, at a relatively low concentration or following washout, increased nerve-mediated contractions. This effect was observed after application of $10^{-6}$ and $10^{-5}$ g/ml in the case of hypogastric nerve (preganglionic) stimulation, and during and after application of $10^{-5}$ g/ml in the case of transmural (postganglionic) stimulation. The above-mentioned depressant effects of ketamine on both types of contraction would have counteracted these stimulatory effects, and vice versa. Nevertheless, comparison of the minimal effective concentrations required to produce a stimulatory effect with pre- and postganglionic stimulation indicates that ketamine has a greater effect on contractions following preganglionic nerve stimulation than on contractions produced by postganglionic nerve stimulation. The mechanism of stimulatory response to ketamine may be related to persistent membrane depolarization in the frog sympathetic ganglion cells,[11] inhibition of reuptake of norepinephrine by adrenergic nerve terminals,[13-15] or alteration in the intracellular disposition of cyclic AMP producing positive inotrophic effects in heart muscle.[21]

Similar dual actions of ketamine, depression at higher doses and excitation at lower concentrations, or transient depression followed by a pressor response, have also been reported to occur in the cardiovascular system of dogs[4, 22] and pithed rats.[23] The excitatory effects appear to predominate in man.[1-3] The stimulatory effect found in the present study, however, does not appear to correspond to that found by others in man[1-3] and animals.[4, 22, 23] It remains difficult to explain why this effect occurred with such a long delay after start of the application and why it persisted for so long during washout. Perhaps ketamine penetrates the cell membrane and remains inside the cells for a long time during washout, thereby producing a prolonged stimulatory effect from inside the cells.

In conclusion, ketamine revealed a dual action on the nerve-mediated contractions of guinea pig vas deferens in vitro, depending on its concentration and time course. Whether showing enhancement or depression, the effects were greater following preganglionic nerve stimulation than following postganglionic nerve stimulation. The site of action of ketamine includes sympathetic ganglia.

## ACKNOWLEDGMENT

The authors are grateful to Dr. T. Isa for his valuable comments on this study.

## REFERENCES

1. Domino EF, Chodoff P, Corssen G: Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6:279-291, 1965
2. Corssen G, Domino EF: Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg 45:29-39, 1966
3. Corssen G, Miyasaka M, Domino EF: Changing concepts in pain control during surgery: dissociative anesthesia with CI-581. Anesth Analg 47:746-758, 1968
4. Traber DL, Wilson RD, Priano LL: Differentiation of the cardiovascular effects of CI-581. Anesth Analg 47:769-778, 1968
5. Dowdy EG, Kaya K: Studies of the mechanism of cardiovascular responses to CI-581. Anesthesiology 29:931-943, 1968
6. Slogoff S, Allen GW: The role of baroreceptors in the cardiovascular response to ketamine. Anesth Analg 53:704-707, 1974
7. Traber DL, Wilson RD: Involvement of the sympathetic nervous system in the pressor response to ketamine. Anesth Analg 48:248-252, 1969
8. Traber DL, Wilson RD, Priano LL: Blockade of the hypertensive response to ketamine. Anesth Analg 49:420-426, 1970
9. Traber DL, Wilson RD, Priano LL: The effect of beta-adrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg 49:604-613, 1970
10. Traber DL, Wilson RD, Priano LL: The effect of alpha-adrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg 50:737-742, 1971
11. Gallagher JP, Dun N, Higashi H, et al: Actions of ketamine on synaptic transmission in frog sympathetic ganglia. Neuropharmacology 15:139-143, 1976
12. Clanachan AS, McGrath JC: Effects of ketamine on the peripheral autonomic nervous system of the rat. Br J Pharmacol 58: 247-252 1976
13. Nedergaard OA: Cocaine-like effect of ketamine on vascular adrenergic neurons. Eur J Pharmacol 23:153-161, 1973
14. Montel H, Starke K, Gorlitz BD, et al: Tierexperimentelle Untersuchungen zur Wirkung des Ketamins auf periphere sympathische Nerven. Anaesthetist 22:111-116, 1973
15. Hill GE, Wong KC, Shaw CL, et al: Interactions of ketamine with vasoactive amines at normothermia and hypothermia in the isolated rabbit heart. Anesthesiology 48:315-319, 1978
16. Hukovic S: Responses of the isolated sympathetic nerve-ductus deferens preparation of the guinea pig. Br J Pharmacol 16:188-194, 1961
17. Bentley GA, Sabine JR: The effects of ganglion-blocking and postganglionic sympatholytic drugs on preparations of guinea pig vas deferens. Br J Pharmacol 21:190-201, 1963
18. Birmingham AT, Wilson AB: Preganglionic and postganglionic stimulation of the guinea pig isolated vas deferens preparation. Br J Pharmacol 21:569-580, 1963
19. Amaki Y, Nagashima H, Radnay PA: Ketamine interaction with neuromuscular blocking agents in the phrenic nerve-hemidiaphragm preparation of the rat. Anesth Analg 57:238-243, 1978
20. Lundy PM, Gowdey CW, Colhoun EH: Further experimental evidence for a smooth muscle depressant effect of ketamine. Arch Int Pharmacodyn Ther 216:57-62, 1975
21. Adams HR, Parker JL, Mathew BP: Influence of ketamine on inotropic and chronotrophic responsiveness of heart muscle. J Pharmacol Exp Ther 201:171-183, 1977
22. Nakajima T, Azumi T, Iwasaki H, et al: Biphasic response of the SA node of the dog heart in vivo to selective administration of ketamine. Arch Int Pharmacodyn Ther 228:108-117, 1977
23. Clanachan AS, McGrath JC, MacKenzie JE: Cardiovascular effects of ketamine in the pithed rat, rabbit and cat. Br J Anaesth 48:935-939, 1976

ANESTH ANALG
59:50-54, 1980

# Intraocular Pressure during Enflurane and Neurolept Anesthesia in Adult Patients Undergoing Ophthalmic Surgery

**Julia V. Presbitero, MD,* Richard S. Ruiz, MD,† Benjamin M. Rigor, Sr., MD,‡ John Huey Drouilhet, MD,§ and Edward L. Reilly, MD‖**

---

PRESBITERO, J. V., RUIZ, R. S., RIGOR, B. M., SR., DROUILHET, J. H., AND REILLY, E. L.: Intraocular pressure during enflurane and neurolept anesthesia in adult patients undergoing ophthalmic surgery. Anesth Analg 59:50–54, 1980.

The effects of neurolept and enflurane anesthesia on intraocular pressure (IOP) were studied in 20 patients undergoing elective ophthalmic surgery. Ten received neurolept and ten enflurane anesthesia. Continuous EEG tracings recorded the level of anesthesia. IOP was measured before and at intervals during anesthesia at varying concentrations of enflurane and incremental doses of fentanyl.

During level I neurolept anesthesia IOP increased from control values of 18.10 ± 0.93 mm Hg (mean ± SEM) to 19.50 ± 1.65 mm Hg, but decreased to 14.55 ± 0.84 mm Hg during level II and to 12.29 ± 1.13 mm Hg during level III anesthesia. During enflurane anesthesia IOP decreased from control values of 19.00 ± 1.44 mm Hg (mean ± SEM) to 14.50 ± 1.60 mm Hg during level I, 14.10 ± 1.04 mm Hg during level II, and 11.60 ± 1.46 mm Hg during level III anesthesia. The increase in IOP during neurolept level I anesthesia was not statistically significant but the decreases in IOP from control values during levels II and III anesthesia were statistically significant. Decreases in IOP from control values were statistically significant at all levels of enflurane anesthesia. There was, however, no statistical significance between the differences in IOP values during levels II and III neurolept anesthesia, nor between levels I, II, and III enflurane anesthesia. The differences in the mean IOP values between neurolept and enflurane anesthesia were statistically significant only during EEG level I anesthesia.

**Key Words:** ANESTHETICS, Volatile: enflurane; ANESTHETICS, Intravenous: Innovar; EYE: intraocular pressure.

---

THE CONTROL of intraocular pressure (IOP) is often of prime importance in intraocular surgical procedures.[1] Anesthetics that influence IOP have a decisive role in providing desirable operative conditions.

Most inhalation anesthetic agents decrease IOP in man.[2-4] The decrease appeared to be directly related to the depth of anesthesia. Many anesthetics, such as chloroform, hydroxydione sodium succinate, and trichloroethylene,[2] as well as the explosive agents, diethyl ether, and cyclopropane[4] have, however, little or no place in anesthesia for ophthalmic procedures today. On the other hand, halothane is useful in ophthalmic surgery not only because it lowers IOP, but also because it is unassociated with delirium and excitement during recovery[6]; many, however, would

---

* Associate Professor, Department of Anesthesiology.
† Professor and Chairman, Department of Ophthalmology.
‡ Professor and Chairman, Department of Anesthesiology.
§ Instructor, Department of Ophthalmology.
‖ Associate Professor, Department of Psychiatry and Behavioral Sciences; Chief EEG and Clinical Neurophysiology Laboratory.

Supported in part by a grant from the Houston Eye Fund.
Received from the Hermann Hospital and The University of Texas Medical School, 6431 Fannin, Houston, Texas 77030. Accepted for publication July 29, 1979.
Reprint requests to Dr. Fresbitero.

prefer not to administer it to patients with liver disease. The effect of intravenous anesthetics on IOP is less clear. Ivankovic and Lowe[3] documented a small decrease in IOP following anesthesia with Innovar during orthopedic and plastic procedures, whereas ketamine has been reported to cause either a slight increase[7] in IOP, or no change.[8]

Ophthalmic surgeons in our institution have observed that tension of the ocular wall during neurolept anesthesia appears to increase and so impede closure of ocular walls, especially during corneal transplant procedures. This has raised questions on the use of neurolept anesthesia in intraocular surgery.

In this study we determined changes in IOP occurring during ophthalmic operations and compared the effects of enflurane and neurolept anesthesia in adult patients. These two anesthetics are predominantly used in intraocular surgery in our institution.

## Materials and Methods

Twenty patients, A.S.A. physical status I to III, ranging in age from 32–80 years scheduled for elective eye surgery at Hermann Hospital were studied. The nature of the study was explained to each patient and written informed consent obtained. The experimental protocol was approved by the University Committee on the Protection of Human Subjects.

All patients were premedicated with 0.4 mg of atropine sulfate. Four patients who showed marked anxiety were also premedicated with 50 to 75 mg of meperidine hydrochloride. Medications were given intramuscularly 60 minutes prior to induction of anesthesia.

Electroencephalographic (EEG) recordings were taken during the procedure. Silver chloride electrodes (Grass E5H) were applied according to the international 10-20 system with the first electrodes 10% of the distance from nasion (bridge of the nose) to inion (external occipital protuberance) and with additional electrodes at 20% intervals of the distance between these two points. In order to provide the surgeon a wider operative field, the anterior frontal polar electrodes (Fp1 and Fp2) were placed 20% from the nasion rather than 10%. The electrodes were attached with gauze and collodion. Recordings were obtained on a 16-channel Grass model 8 EEG machine. During most of the procedure a bipolar montage in the anterior-posterior direction was employed. Either two or four channels of the recorder involving the frontal-cerebral and parietal-occipital activity were linked from the EEG amplifiers to a Nicolet Med-80 computer. Fast Fourier analysis of the EEG activity was done, and a print-out was made of the respective power levels with a simultaneous plot of this activity in each of the traditionally evaluated EEG bands. EEG recordings started prior to induction of anesthesia and continued throughout the procedure until the patient was ready for transfer to the recovery room. EEG tracings during anesthesia were interpreted according to the criteria of Martin et al[9] and Neigh et al.[10]

Upon the patient's arrival in the operating room, topical 0.5% tetracaine hydrochloride ophthalmic solution was applied to the eye not undergoing surgery. Baseline measurements of the IOP were taken in the nonoperative eye with an EMT (Electro-Medical Technology) Digital Applanation Tonometer. Two equal readings from four read-outs were taken as the intraocular pressure.

Subsequent IOP readings were taken 10 to 15 minutes following endotracheal intubation and at 30-minute intervals until termination of the operation. All tonomeric readings were obtained by the same person. Care was taken to avoid bucking or straining, especially during the readings. The results were analyzed using a Student's paired *t*-test to determine the significance of differences in IOP between control and the various anesthetic levels. An unpaired Student's *t*-test was used for determining the statistical significance of differences between the mean IOP values when the two anesthetics were associated with the same anesthetic EEG level.

Respiration was controlled. Arterial blood samples withdrawn from the radial artery during the surgical procedure showed pH, $P_{CO_2}$ and $P_{O_2}$ values ranging from 7.35 to 7.48, 32 to 44 torr, and 130 to 465 torr, respectively. Blood pressure and pulse rate were recorded at 5-minute intervals. Esophageal temperature and electrocardiographic tracings were displayed continuously on Monatherm (La Barge, Inc.) and Roche-Parameton II machines, respectively. Body temperatures remained normal in all patients.

Half the patients had neurolept anesthesia, half enflurane anesthesia. This choice was made on a random basis. Pancuronium was used for muscle relaxation.

### Group 1: Neurolept Anesthesia

Neurolept anesthesia was induced by intravenous Innovar 1 ml/12 to 20 kg of body weight. The dosage was adjusted to maintain blood pressure and heart rate within satisfactory ranges. When induction was prolonged, sodium thiopental was used. Pancuronium, 1.0 mg/10 kg IV, was given for endotracheal intubation. Small incremental doses of the muscle relaxant were subsequently administered to allow mechanical or manual control of ventilation.

For maintenance of anesthesia, fentanyl was injected in 0.05-mg doses at approximately 15- to 20-minute intervals, with 60% nitrous oxide supplementation. The first IOP reading during anesthesia was taken prior to addition of nitrous oxide. At the end of the procedure, atropine, neostigmine, and naloxone were used to reverse the muscle relaxant and the narcotic.

### Group 2: Enflurane Anesthesia

Anesthesia was induced with thiopental sodium, 3 mg/kg, and endotracheal intubation performed after pancuronium, 1.0 mg/10 kg. Enflurane in $O_2$ was then started. Anesthesia was maintained with enflurane as the sole anesthetic agent. Respiration was controlled. At the termination of the operation, pancuronium was reversed with atropine and neostigmine and extubation performed upon restoration of normal respiration.

## Results

### Neurolept Anesthesia

During level I anesthesia there was a mean increase in IOP to 19.5 ± 1.65 mm Hg (mean ± SEM) from mean control values of 18.1 ± 0.93 mm Hg (Table 1). This change in IOP was not statistically significant. On the other hand, there were statistically significant decreases in IOP during EEG levels II ($p < 0.001$) and III ($p < 0.01$) anesthesia to 14.6 ± 0.84 mm Hg (mean ± SEM) and 12.3 ± 1.13 mm Hg, respectively. The differences in IOP between these two levels and EEG level I were also statistically significant ($p < 0.001$), although the difference in IOP values during EEG levels II and III was not significant. IOP values with and without nitrous oxide supplementation were not significantly different at any levels of anesthesia (Table 1).

**TABLE 1**

**Intraocular Pressure (mm Hg) during Neurolept Anesthesia**

| Case no. | Control | Level I anesthesia | Level II asesthesia | Level III anesthesia |
|---|---|---|---|---|
| 1 | 21 | 20 | 19* | 17* |
| 2 | 19 | | 15* | 12* |
| 3 | 20 | | 14* | 13 |
| 4 | 13 | | 12* | 9* |
| 5 | 15 | | 13* | |
| 6 | 17 | | 11* | 9 |
| 7 | 19 | | 16* | 11 |
| 8 | 22 | 23* | | |
| 9 | 21 | 20* | 17* | 15 |
| 10 | 16 | 15* | 14 | |
| Mean | 18.1 | 19.5 | 14.6 | 12.3 |
| SEM | 0.93 | 1.65 | 0.84 | 1.13 |

* Supplemented with 60% $N_2O$.

### Enflurane Anesthesia

Inhaled concentrations of 1% to 1.7% enflurane anesthesia were associated with EEG level I anesthesia, 1.75% to 2.5% with level II, and 3% to 3.3% with level III. The decrease in IOP from mean control values of 19.0 ± 1.44 mm Hg (mean ± SEM) before induction of anesthesia to 14.5 ± 1.60 mm Hg during EEG level I was statistically significant ($p < 0.005$) (see Table 2). The differences between control values of IOP and those observed during EEG levels II and III were also statistically significant ($p < 0.001$). The decreases in IOP values during level III anesthesia in relation to IOP values during EEG levels I and II were not significant. Likewise IOP values during EEG level II anesthesia were not significantly different from those observed during EEG level I anesthesia.

Mean IOP during EEG level I enflurane anesthesia was significantly different from mean IOP during neurolept EEG level I anesthesia ($p < 0.001$). However, mean IOP values during EEG level II and III enflurane anesthesia were not significantly different from mean IOP values during comparative levels of neurolept anesthesia.

## Discussion

The first study on the effect of neurolept anesthesia on IOP was performed by Ivankovic and Lowe[3] who recorded 12% decrease in IOP following an induction dose of Innovar (1 ml/8 kg).

The influence of enflurane anesthesia on IOP was first studied by Radtke and Waldman[4] in patients 6

**TABLE 2**

**Intraocular Pressure (mm Hg) during Enflurane Anesthesia**

| Case no. | Control | Level I anesthesia | Level II anesthesia | Level III anesthesia |
|---|---|---|---|---|
| 1 | 17 | | 15 | |
| 2 | 26 | 21 | 16 | 10 |
| 3 | 11 | 10 | 9 | |
| 4 | 15 | 11 | 9 | 8 |
| 5 | 19 | 16 | 15 | |
| 6 | 21 | | 19 | |
| 7 | 23 | | 17 | 16 |
| 8 | 24 | | 16 | 14 |
| 9 | 16 | 14 | 12 | 10 |
| 10 | 18 | 15 | 13 | |
| Mean | 19.0 | 14.5 | 14.1 | 11.6 |
| SEM | 1.44 | 1.60 | 1.04 | 1.46 |

to 19 years of age spontaneously breathing 3% to 5% enflurane, but other factors which influence IOP were not controlled. They found a mean decrease in IOP of 4 mm Hg (21%). Runciman et al[11] standardized the conditions of their study but confined their investigation to the effect of 1% enflurane anesthesia supplemented by 60% nitrous oxide, and found a mean decrease of 40%.

In the present study varying concentrations of enflurane in $O_2$ were employed as the sole anesthetic agent in patients having enflurane anesthesia. The effects of incremental doses of fentanyl or increasing concentration of enflurane on anesthetic depth and IOP were observed throughout the operative procedure.

We limited the variables that could influence IOP during enflurane and neurolept anesthesia. To do this, in 16 patients premedication was limited to atropine, which, in the doses used, has no effect on intraocular pressure.[12] Four patients were given meperidine due to marked anxiety. Neuromuscular relaxation was provided by pancuronium which has been reported to cause either no significant change[13] or a small but transient decrease in IOP lasting three minutes[14] to 8 minutes.[15] To avoid this possible effect, IOP was measured at least 9 minutes after injection of pancuronium. To eliminate the effect of $P_{CO_2}$ on IOP respiration was controlled.

The present studies with enflurane showed statistically significant decreases in IOP from control values during all levels of anesthesia. However, contrary to previous publications, the decreases in IOP were not related to dosage or depth of anesthesia. Our neurolept studies also showed statistically significant dose-unrelated decreases in IOP from control values but only during levels II and III anesthesia. Furthermore the decreases in IOP observed during neurolept levels II and III anesthesia were not statistically different compared to enflurane at similar levels of anesthesia.

The decreases in intraocular pressure observed in this study may be ascribed to several mechanisms. Several investigators[16-19] have described a hypothalamic center controlling intraocular pressure. Under general anesthesia, the hypothalamus, together with the cerebral cortex and related areas of the central nervous system,[20, 21] is depressed. A decrease in IOP may also be due to a decrease in aqueous outflow.[5] The facility of aqueous outflow is expressed as a coefficient and is the reciprocal of the resistance to the outflow. A high coefficient indicates lowered resistance to aqueous outflow. The increase in coefficient of facility of outflow[4] and the curare-like muscular relaxation[22] associated with enflurane anesthesia may contribute to the decrease in IOP. As Al-Abrak and Samuel[13] suggested, the decrease in IOP following curare may, in contrast to what is observed with pancuronium, be due to mechanisms other than extraocular muscular relaxation, e.g., paralysis of ocular smooth muscles. There is no apparent explanation for the uniform decrease in IOP during the different levels of anesthesia under enflurane anesthesia. It is suggested that the factors that influence IOP during enflurane anesthesia exist early in the first level of anesthesia and remain operative throughout deeper levels of anesthesia.

During neurolept anesthesia some of the factors influencing IOP during enflurane anesthesia are not present. The effects of neurolept on aqueous outflow are uncertain. Kornbleuth's group[5] observed an increased coefficient of facility of outflow while a decrease was reported by Ivankovic and Lowe.[3] No curare-like muscular relaxation is provided by the neurolept drugs. Furthermore, use of pancuronium as a muscle relaxant during neurolept anesthesia allows patients to be maintained in the first level of anesthesia, where some degree of straining may occur with surgical stimulation which may increase IOP. In our institution pancuronium has been used in intraocular surgery in adult patients instead of curare which has been reported to cause a significant decrease in IOP[13] because many of our patients have cardiovascular instability. The one patient in this study who showed an increase in IOP in the first level of neurolept anesthesia appeared to be straining during the procedure. Possibly during deeper levels of anesthesia the depression of the central nervous system decreases the IOP to the same extent as that observed under enflurane anesthesia.

In conclusion, during enflurane anesthesia there was a statistically significant decrease in intraocular pressure in all levels of anesthesia. Neurolept anesthesia was associated with significant decreases in intraocular pressure only during EEG anesthesia levels II and III. The decreases in IOP were not related to depth of anesthesia with either anesthetic.

At equivalent levels of anesthesia there was no statistically significant difference between the mean IOP values of the two anesthetics during EEG anesthesia levels II and III. During EEG level I the mean IOP during enflurane anesthesia was significantly lower than during neurolept anesthesia.

## REFERENCES

1. Duncalf D, Rhodes DH Jr: Anesthesia in Clinical Ophthalmol-

ogy. Baltimore, Williams & Wilkins, 1963, p 11
2. Magora F, Collins V: The influence of general anesthetic agents on intraocular pressure. Arch Ophthalmol 66:806–811, 1961
3. Ivankovic AD, Lowe HJ: Influence of methoxyflurane and neurolept anesthesia on intraocular pressure in man. Anesth Analg 48:933–938, 1969
4. Radtke N, Waldman J: The influence of enflurane anesthesia on intraocular pressure in youths. Anesth Analg 54:212–215, 1975
5. Kornbleuth W, Aladjemoff L, Magora F, et al: Influence of general anesthesia on intraocular pressure in man. Arch Ophthalmol 61:84–87, 1959
6. Esposito AC: The role of general anesthesia (halothane) in cataract surgery. South Med J 58:992–995, 1965
7. Corssen G, Hay JE: A new parenteral anesthetic CI-581: its effect on intraocular pressure. J Pediatr Ophthalmol 3:20–23, 1967
8. Peuler M, Glass DD, Arens JF: Ketamine and intraocular pressure. Anesthesiology 43:575–578, 1975
9. Martin JT, Faulconer A Jr, Bickford RG: Electroencephalography in anesthesiology Anesthesiology 20:359–375, 1959
10. Neigh JL, Garman JK, Harp JR: The electroencephalographic pattern during anesthesia with Ethrane. Anesthesiology 35:482–487, 1971
11. Runciman JC, Bowen-Wright RM, Welsh NA, et al: Intraocular pressure changes during halothane and enflurane anaesthesia: Br J Anaesth 50:371–374, 1978
12. de Roeth A Jr, Schwartz H: Aqueous humor dynamics in glaucoma: effect of ganglionic blocking agents and thiopental. Arch Ophthalmol 55:755–765, 1956
13. Al-Abrak MH, Samuel JR: Effects of general anaesthesia in the intraocular pressure in man: comparison of tubocurarine and pancuronium in nitrous oxide and oxygen. Br J Ophthalmol 58:806–810, 1974
14. Smith RB, Leano N: Intraocular pressure following pancuronium. Can Anaesth Soc J 20:742–745, 1973
15. Litwiller RW, Difazio CA, Rushia EL: Pancuronium and intraocular pressure. Anesthesiology 42:750–752, 1975
16. Duncalf D, Weitzner SW: The influence of ventilation and hypercapnea on intraocular pressure during anesthesia. Anesth Analg 42:232–237, 1963
17. von Sallman L, Macri FJ, Wanko T, et al: Some mechanisms of centrally induced eye pressure responses. Am J Ophthalmol 42:130–147, 1956.
18. von Sallman L, Loewenstein O: Responses of intraocular pressure, blood pressure and cutaneous vessels to electric stimulation in the diencephalon. Am J Ophthalmol 39:11–29, 1955
19. Schmerl E, Steinberg B: The role of the diencephalon in regulating ocular tension. Am J Ophthalmol 31:155–158, 1948
20. Harris TAB: Mode of Action of Anaesthetics. Edinburgh, E & S Livingstone Ltd, 1951, pp 380-381
21. Jenkins LC: General Anaesthesia and the Central Nervous System. Baltimore, Williams & Wilkins, 1969, p 153
22. Kennedy R, Galindo A: Neuromuscular transmission in a mammalian preparation during exposure to enflurane. Anesthesiology 42:432–442, 1975

ANESTH ANALG
59:55-57, 1980

# Furosemide Facilitates Recovery of Evoked Twitch Response after Pancuronium

**Isaac Azar, MD,* James Cottrell, MD,† Bhagwandas Gupta, MD,‡ and Herman Turndorf, MD§**

---

AZAR, I., COTTRELL, J., GUPTA, B., AND TURNDORF, H.: Furosemide facilitates recovery of evoked twitch response after pancuronium. Anesth Analg 59:55–57, 1980.

Two groups consisting of 10 A.S.A. class I-II neurosurgical patients each were studied to determine whether patients require greater quantities of pancuronium to maintain paralysis after having been given furosemide, 1 mg/kg. After a standardized barbiturate, narcotic and nitrous oxide induction of anesthesia, pancuronium was given intravenously until twitch response was suppressed by 95%. The study group received in addition furosemide, 1 mg/kg, 10 minutes prior to induction of anesthesia. Mean recovery time from 95% to 50% twitch suppression was 21.8 minutes in the control group and 14.7 minutes in the study group. Urinary output was significantly greater (13.5 vs 674 ml) and serum potassium levels lower (4.05 vs 3.85 meq/L) in the study group during recovery of twitch response. Furosemide, 1 mg/kg, facilitates recovery of evoked twitch response after pancuronium.

**Key Words:** NEUROMUSCULAR RELAXANTS: pancuronium; KIDNEY: furosemide; PHARMACOLOGY: diuretics.

---

WE HAVE noticed that neurosurgical patients given furosemide, 1 mg/kg, appear to require greater quantities of pancuronium to maintain paralysis. The following study was done to determine whether this observation was correct and to quantitate any differences which were seen.

## Method

Two groups of 10 A.S.A. class I-II neurosurgical patients each were anesthetized using a standardized thiopental, nitrous oxide in oxygen, narcotic and relaxant sequence. Arterial and venous pressure, heart rate, pharyngeal temperature, urinary output, serum potassium levels, and quantitated twitch response were monitored. The study group received 1 mg/kg of furosemide 10 minutes before induction of anesthesia.

After thiopental, 4 mg/kg IV, control twitch response of the hand was measured using supramaximal ulnar nerve stimulation at the elbow. A Grass 48 nerve stimulator coupled with constant current and stimulus isolation units was used to deliver current at 0.2 Hz. The hand response was transduced, amplified, and recorded on an E for M VR6 recorder using a specially designed Twitch Box[1] to quantitate the response. A bolus of pancuronium, 0.04 mg/kg, was then administered intravenously and supplemented, as necessary by 0.1-mg increments until twitch response was suppressed by 95%. Recovery times from

---

* Assistant Professor.

† Associate Professor.

‡ Resident.

§ Professor and Chairman.

Received from the Department of Anesthesiology, New York University Medical Center, 560 First Avenue, New York, New York 10016. Accepted for publication August 23, 1979. Presented at the Annual Meeting of the American Society of Anesthesiologists, October 21-25, 1978, Chicago, Illinois.

Reprint requests to Dr. Azar, Department of Anesthesiology, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY 10003.

95% to 75% and to 50% twitch suppression were determined ($T_{95\%-75\%}$ and $T_{75\%-50\%}$, respectively). Paired t-tests were used for statistical analysis.

## Results

Twitch recovery was significantly more rapid in patients given furosemide. Mean recovery time from 95% to 50% twitch depression was 21.8 minutes in the control and 14.7 minutes in the study group. Urinary output was significantly greater and serum potassium levels lower during twitch recovery in the study group. Results are summarized in the Table.

## Discussion

Pancuronium is primarily eliminated unchanged by the kidneys, although a small fraction is metabolized by the liver.[2] The rate of twitch height recovery depends on drug distribution, renal function, body temperature, acid-base and electrolyte balance, drug interaction, and neuromuscular disorders.[3]

Furosemide and other diuretics potentiate the neuromuscular blocking effects of non-depolarizing muscle relaxants. Miller et al[4] reported potentiation of curare in anephric patients after administration of mannitol, 12.5 g, and furosemide, 80 mg, combined. Gessa and Ferrari[5] also found curare potentiation in thiazide-treated rabbits.

Our observation that recovery time from pancuronium is shortened after furosemide appears to contradict these findings. However, significant differences in the methods used may explain this apparent contradiction. We studied patients with normal renal function to whom pancuronium was given during the peak diuretic effect of furosemide. Others studied anephric patients[4] or animal preparations.[5]

**TABLE**

**Effect of Furosemide on $ED_{95\%}$, Recovery Rate of Twitch Response, Urinary Output, and Serum Potassium after Pancuronium (mean ± SE)**

| | Control (n = 10) | Study (n = 10) | p |
|---|---|---|---|
| Mean $ED_{95\%}$ of pancuronium (mg/kg) | 0.04 ± 0.00 | 0.05 ± 0.01 | NS |
| Mean recovery time $T_{95\%-75\%}$ (min) | 14.10 ± 0.27 | 9.30 ± 0.79 | <0.0005 |
| Mean recovery time $T_{75\%-50\%}$ (min) | 7.70 ± 0.60 | 5.40 ± 0.19 | <0.0025 |
| Mean urinary output $T_{95\%-75\%}$ (ml) | 13.50 ± 2.54 | 674.0 ± 120.0 | <0.0005 |
| Mean serum $K^+$ at $5_{50\%}$ (meq/L) | 4.05 ± 0.18 | 3.85 ± 0.20 | <0.05 |

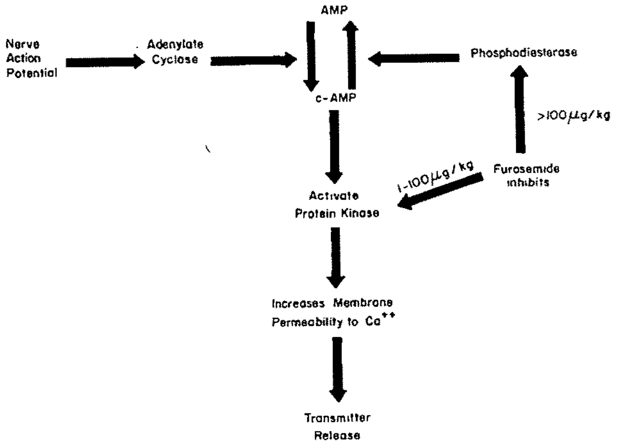


FIGURE. Basis of a possible dual effect of furosemide at the neuromuscular junction.

The enhancement of twitch recovery by furosemide may be due to a direct effect on the neuromuscular junction, an indirect effect altering serum potassium levels, or an increased pancuronium urine excretion rate.

It has been suggested|| that in the cat small doses (1 to 100 μg/kg IA) of furosemide reduce calcium influx at the motor nerve ending, possibly by blocking a protein kinase (Figure). This would inhibit muscular contractions and potentiate non-depolarizing relaxants. Extremely large doses (100 μg/kg IA) of furosemide inhibit phosphodiesterase and thereby possibly increase the level of nerve ending cyclic AMP. This facilitates calcium influx, enhances muscular contraction, and antagonizes non-depolarizing muscle relaxants. Gessa and Ferrari[5] described this biphasic effect using thiazides in rabbits. Chlorothiazide, 100 mg/kg IV, enhanced curare and 300 mg/kg antagonized it. The dose of furosemide we used (1 mg/kg) is in the range that has been found in animal preparation to enhance the neuromuscular junction transmission.|| That could be one explanation for the facilitated twitch recovery in our study.

Chronic administration of diuretics may cause hypokalemia which can potentiate non-depolarizing muscle relaxants,[6] but acute changes in serum potassium levels have not been shown to have a significant

---

|| Ham J, Scapaticci KA, Dretchen KL, et al: Effect of furosemide on neuromuscular transmission. Abstracts of Scientific Papers, of American Society of Anesthesiologists Annual Meeting, 1977, pp 471-472.

effect on reactivity of non-depolarizing relaxants. In our patients who were given furosemide mean serum potassium was significantly lower than in the control group, but because it was an acute change, it probably played no role.

Although pancuronium is primarily excreted by the kidneys, the effect of diuresis on its excretion rate has not been studied. Furosemide could possibly increase pancuronium excretion rate by increasing renal blood flow and glomerular filtration rate. Furosemide does indeed increase renal blood flow and glomerular filtration rate to a small extent.[7] It is possible that pancuronium administration coincided in our study with the peak effect of furosemide on renal blood flow and glomerular filtration rate and thus pancuronium excretion rate increased.

## REFERENCES

1. Azar I, Wu W, Turndorf H: Twitch Box: a new device to monitor neuromuscular blockade. Med Instrum 12:92–93, 1978
2. Agoston S, Vermeer GA, Kersten LW, et al: The fate of pancuronium bromide in man. Acta Anaesthesiol Scand 17: 267–275, 1973
3. Miller RD: Antagonism of neuromuscular blockade. Anesthesiology 44:318–329, 1976
4. Miller RD, Sohn YJ, Matteo RS: Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. Anesthesiology 45:442–445, 1976
5. Gessa GL, Ferrari W: Influence of chlorothiazide and acetazolamide on neuromuscular transmission in mammals. Arch Int Pharmacodyn Ther 144:258–268, 1963
6. Miller RD, Roderick LL: Diuretic induced hypokalemia, pancuronium neuromuscular blockade and its antagonism by neostigmine. Br J Anaesth 50:541–544, 1978
7. Kim KE, Onesti G, Moyer JH, et al.: Ethacrynic acid and furosemide: diuretic and hemodynamic effects and clinical uses. Am J Cardiol 27:407–413, 1971

---

## Drug Delivery Kinetics in Intravenous Systems

The kinetics of drug delivery were studied under conditions of varying intravenous flow rates and varying sites of drug administration into an intravenous system. The rate of drug delivery from the intravenous system was dependent upon the intravenous flow rate and site of injection of the drug into the intravenous system. Under conditions of slow intravenous flow rates (3 ml/hour) there was the expected time delay required for the drug to begin to be infused but an unanticipated protracted time required for actual completion of the drug infusion. Calculation of theoretical drug blood levels based on the results of these intravenous studies revealed very different blood levels of drug at respective times, including different peak concentrations, depending on the intravenous flow rate and site at which the drug was injected into the system. Failure to appreciate the effects of slow intravenous rates and remote intravenous injection sites on actual rates of drug administration can adversely affect pharmacokinetic decisions and conceivably influence therapeutic success or failure. *(Gould T, Roberts RJ: Therapeutic problems arising from the use of the intravenous route for drug administration. J Pediatr 95:465–471, 1979)*

ANESTH ANALG
59:58-60, 1980

# Physostigmine-Atropine Solution Fails to Reverse Diazepam Sedation

**Jeffrey G. Garber, DMD,* Alan Jay Ominsky, MD,† Fredrick K. Orkin, MD‡ and Peter Quinn, DMD§**

---

GARBER, J. G., OMINSKY, A. J., ORKIN, F. K., AND QUINN, P.: Physostigmine-atropine solution fails to reverse diazepam sedation. Anesth Analg 59:58–60, 1980.

Patients undergoing dental extraction under intravenous diazepam sedation were studied to determine whether physostigmine, a cholinesterase inhibitor, reverses diazepam-induced sedation. A modified Bender-Gestalt Dot Test was used to measure psychomotor function. Patient self-assessment of recovery and a surgeon's independent assessment of recovery were scored on a 0 to 10 measured scale before and after administration of either a physostigmine-atropine mixture (nine patients) or saline (12 patients).

The physostigmine-atropine mixture did not significantly speed recovery or improve psychomotor function when compared with normal saline. The results indicate that, in contradiction to previous case reports, the analeptic effect of physostigmine may be specific for anticholinergic drugs.

**Key Words:** ANTAGONISTS, Miscellaneous: physostigmine; HYPNOTICS, Benzodiazepines: diazepam.

---

INTRAVENOUS diazepam enjoys widespread use for outpatient surgical sedation. While recovery times are variable, prolonged sedation and central depression have been reported.[1, 2] Recent interest in the use of physostigmine, a cholinesterase inhibitor, to reverse sedative drugs[3-5] stimulated our investigation of its use in reducing recovery time following intravenous diazepam.

Although the site of action of diazepam is not completely understood, it is thought to interfere with interneuronal transmission within the spinal cord and in supraspinal structures within the limbic system.[6] The sedation or calmness achieved with diazepam is probably due to its action on the amygdala, that part of the limbic system which serves as a relay area for the expression of emotion.

Physostigmine inhibits the destruction of acetycholine by acetylcholinesterase. This allows accumulation of acetycholine at the neuroreceptor sites and leads to an increase in cholinergic stimulation. Unlike quaternary anticholinesterases such as neostigmine, physostigmine crosses the blood-brain barrier, thereby acting both centrally and peripherally. It has been used to reverse central nervous system depression induced by a variety of agents with anticholinergic properties.[7] These drugs include the belladonna alkaloids (e.g., scopolamine), phenothiazines (e.g., chlorpromazine), tricyclic antidepressants (e.g., imipramine), and butyrophenones (e.g., droperidol).

Although diazepam has no known central anticholinergic effects, reports have indicated reversal by diazepam in cases of delirium associated with diazepam.[5] It has been contended that physostigmine also may have a nonspecific analeptic effect and hence might be useful in patients who have received drugs without demonstrable anticholinergic properties.[1] It is with this in mind that the current study was undertaken.

---

* Assistant Professor of Anesthesia, School of Medicine; Assistant Professor of Pharmacology and Oral Surgery, School of Dental Medicine.

† Associate Professor of Anesthesia and Psychiatry.

‡ Assistant Professor of Anesthesia and Research Medicine.

§ Chief Resident in Oral Surgery, School of Dental Medicine.

Received from the Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication August 20, 1979.

Reprint requests to Dr. Garber, Department of Anesthesia, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104.

## Methods

Twenty-one A.S.A. physical status class I patients undergoing routine dental extractions with intravenous diazepam sedation and local anesthesia participated in this double-blind study. Twelve control patients received a 3-ml solution of saline and nine test patients received a 3-ml solution containing 2 mg of physostigmine and 1 mg of atropine intravenously at the end of the surgical procedure. These patients were assigned randomly into one of the two experimental groups by picking one of 24 sealed, coded envelopes. Informed consent was obtained prior to initiation of treatment. All patients were given intravenous diazepam incrementally at a rate of 5 mg/min until Veril's eye sign (half-lid ptosis) was observed (Table 1). After satisfactory local anesthesia was obtained, the oral surgical procedures were performed. No procedure lasted longer than 15 minutes.

Two measures of recovery were employed. One involved psychomotor testing via a modifed Bender-Gestalt test. The other involved independent ratings of wakefulness by the patient and the surgeon.

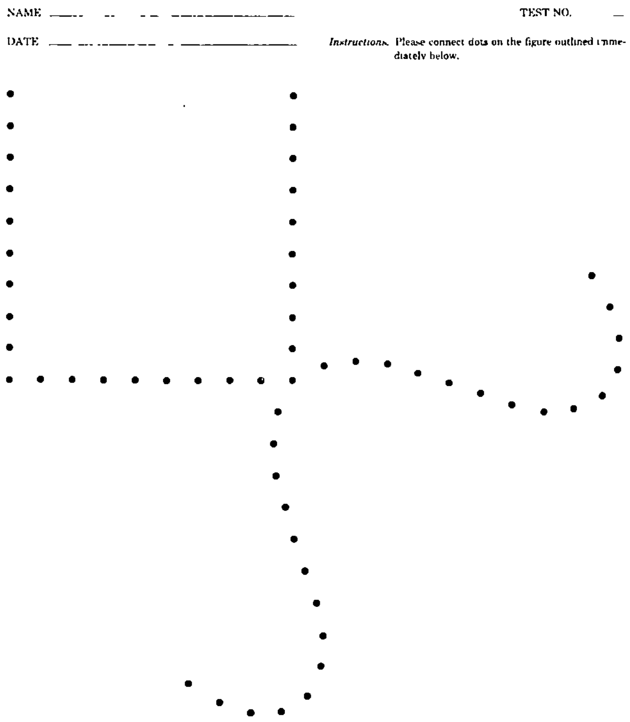
To measure psychomotor function during recovery from diazepam sedation, a portion of the Bender Motor Gestalt test as modified by Newman, Trieger, and Miller[8] was administered to each patient four times. The test was given preoperatively, immediately postoperatively, and at 5- and 15-minute intervals following injection of the unknown solution. The tests were given in the sitting position. Patients were asked to simply connect the dots in the figure as shown (Figure). The number of dots completely missed on the Bender-Gestalt test was counted. All tests were graded by the same examiner. Recovery within each of the two test groups was based on a change from the preoperative test in the mean number of dots missed when measured during the three postoperative time periods (Table 2). Data from both groups were analyzed using a chi square test; $p < 0.05$ was considered statistically significant.

The second assessment, done independently by patients and by the oral surgeon, rated subjective estimates of recovery. Patients were asked to record on a measured scale (0 to 10) their feelings of wakefulness. Independently, the oral surgeon was asked to assess the patient's state of recovery using the same scale. The data were read off these scales to the nearest integer. These tests were given immediately postoperatively and again 5 minutes after administration of one of the test solutions. The subjective tests for both patients and surgeons were graded by recording the differences in scores before and after the administration of the test solution. $p < 0.05$ in a two-tailed Mann-Whitney U-test[11] was taken as the level of statistical significance in evaluating these results.

**TABLE 1**

**Patient Groups and Diazepam Dose**

| Group | No. of subjects | Mean weight | Mean dose of diazepam | Diazepam dose |
|---|---|---|---|---|
| | | *kg* | *mg* | *mg/kg* |
| Physostigmine-atropine | 9 | 66.5 | 17.2 | 0.26 |
| Saline | 12 | 68.4 | 16.7 | 0.24 |



NAME ____________ TEST NO. ___

DATE ____________

*Instructions.* Please connect dots on the figure outlined immediately below.

FIGURE. Modified Bender-Gestalt test used for evaluation of psychomotor function.

**TABLE 2**

**Change in Total Number of Dots Missed at Each Time Period***

| Group | Period | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Physostigmine-atropine | 67 | 50 | 43 |
| Saline | 123 | 101 | 59 |

* Values are preoperative vs postoperative at three time periods: (1) immediately postoperatively; (2) immediately postoperatively + 5 minutes; and (3) immediately postoperatively + 15 minutes.

## Results

The diazepam doses sufficient to achieve half-lid ptosis are presented in Table 1.

The Bender-Gestalt test, as expected, showed fewer misses in both control and in experimental patients as a function of time following surgery (Table 2). However, when the groups were compared, at each of the time periods the total number of dots missed was not significantly different (chi squared = 2.26). The median scores in the subjective recovery scale immediately postoperatively were 5.75 in the control groups and 6.00 in the experimental group. Note that higher scores indicated an increased feeling of recovery. Five minutes after the administration of the test solution, the median scores were 8.25 in the control group and 6.00 in the experimental group. U values from the patient's self-assessment as obtained from the Mann-Whitney U-test were 26 indicating statistical significance for a two-tailed test at the $p = 0.05$ confidence level. Median scores from the surgeon's subjective evaluation of recovery immediately postoperatively showed values of 5.50 and 6.00 in the control and test groups, respectively. Five minutes later, following "reversal," the median score was 7.75 in control patients as compared to 6.00 in the experimental group.

Results from the surgeon's assessment of recovery likewise showed that participants in the control group scored significantly higher on their rating scales than did those in the experimental groups. U values from this groups were also ≤26 indicating statistical significance.

## Discussion

Physostigmine has previously been shown to be effective in reversing the central anticholinergic action of such drugs as scopolamine.[10] Since diazepam has no known central anticholinergic effect, case reports suggesting the ability of physostigmine to reverse diazepam delerium or overdose have led to the belief that physostigmine may have a nonspecific analeptic effect on this drug.[1, 5] If indeed physostigmine were effective in hastening the recovery of sedation achieved with diazepam, it would be very useful in outpatient anesthesia. However, our data indicate that a mixture of physostigmine and atropine does not speed the recovery process or improve psychomotor function and, hence, our data suggest that physostigmine does not have an analeptic effect on diazepam-induced sedation. Indeed, when used in combination with atropine (as it must be to avoid unpleasant muscarinic effects), physostigmine significantly delayed the recovery process. Atropine, on the other hand, when used to prevent the muscarinic effects of physostigmine may exert anticholinergic effects, e.g., large doses of atropine cause sedation and have a synergistic sedative effect when combined with other sedative drugs.[9] It may be that while physostigmine reverses most of the the central nervous system depression produced by atropine, it does not reverse all of it. This may account for the observed increase in sleepiness and decrease in psychomotor performance in the patients that received the atropine-physostigmine mixture.

### REFERENCES

1. Larson GF, Hurlbert BJ, Wingard DW: Physostigmine reversal of diazepam-induced depression. Anesth Analg 56:348–351, 1977
2. Gale GD: Recovery from methohexitone, halothane and diazepam. Br J Anaesth 48:691–697, 1976
3. Smith DB, Clark RB, Stephens SR, et al: Physostigmine reversal of sedation in parturients. Anesth Analg 55:478–480, 1976
4. Bidwal AV, Cornelius LR, Stanley TH: Reversal of Innovar-induced postanesthetic somnolence and disorientation with physostigmine. Anesthesiology 44:249–252, 1976
5. DiLiberti J, O'Brien ML, Turner T: The use of physostigmine as an antidote in accidental diazepam intoxication. J Pediatr 86: 106–107, 1975
6. Dundee JW, Keilty SR: Diazepam. Int Anesthesiol Clin 7:91–121, 1969
7. Rumach BH: Anticholinergic poisoning: treatment with physostigmine. Pediatrics 52:449, 1973
8. Newman MG, Trieger N, Miller JC: Measuring recovery from anesthesia—a simple test. Anesth Analg 48:136–140, 1969
9. Smith DS, Orkin FK, Gardner SM, et al: Prolonged sedation in the elderly after intraoperative atropine administration. Anesthesiology. 51:348–349, 1979
10. DuVoisin RC, Katz R: Reversal of central anticholinergic syndrome in man by physostigmine. JAMA 206:1963–1965, 1968
11. Roscoe JG: *Fundamental Research Statistics for the Behavioral Sciences.* Holt, Rinehart & Winston, 1975, 2nd edition, pp 230–236

ANESTH ANALG
59:61-64, 1980

# Detection of Fluorinated Anesthetic Metabolites by Sodium Fusion

**Joseph J. Soltis, BA,* and A. Jay Gandolfi, PhD†**

SOLTIS, J. J., AND GANDOLFI, A. J.: Detection of fluorinated anesthetic metabolites by sodium fusion. Anesth Analg 59:61-64, 1980.

A method is reported which utilizes a sodium fusion reaction to decompose organofluorine compounds and yield ionic fluoride which may then be quantified with a specific ion electrode. The method is simple, quick, sensitive, and applicable to fluorinated anesthetic metabolites.

**Key Words:** MEASUREMENT TECHNIQUES: fluorinated metabolites; BIOTRANSFORMATION (DRUG): fluorinated metabolites.

PREVIOUS studies concerning the metabolism of volatile fluorinated anesthetics to organic fluoride metabolites have used oxygen combustion techniques to cleave the carbon-fluorine bond and allow the fluoride to be quantified.[1-3] These techniques are cumbersome, require specific glassware, and often produce interfering substances which register on the specific ion electrode.[4] Elving and Ligett[5] have reported a technique that utilizes alkali metal fusion to reductively decompose organohalogen compounds and liberate halide ions which may be quantified by a number of techniques. In this report we describe a modification of this techique which allows us to rapidly detect and quantify fluorinated anesthetic metabolites in biologic samples.

## Methods

### Preparation of Standards

Trifluoroacetic acid was chosen as indicative of the terminal metabolites of volatile fluorinated anesthetics, since it is one of the end-products of halothane, isoflurane, and fluoroxene biotransformation.[6] In addition, fenfluramine (three C-F bonds) was chosen as a nonvolatile fluorinated compound for further confirmation of this technique.

To determine the linearity and range of the sodium fusion technique, aliquots of alkaline standard solutions of sodium trifluoroacetate and fenfluramine (0.02 to 4.0 µmoles) were added to screw-cap culture tubes. The samples were then lyophilized to dryness for subsequent analysis of organic fluoride.

For the determination of the efficiency of this technique with various biologic samples, sodium trifluoroacetate solutions (0 to 13.5 µmoles) were added to equal volumes (0.2 ml) of water, 0.05 M phosphate buffer at pH 7.4, blood, urine, and hepatic microsomal suspensions (5 mg of protein per milliliter) in screw-cap culture tubes. The samples were made alkaline by adding 50 µl of 0.1 N NaOH and lyophilized to dryness for organic fluoride analysis.

For the determination of the influence of sodium fusion on ionic fluoride detection, known amounts of sodium fluoride (0 to 10 µmoles) were added to blank solutions of water, phosphate buffer, urine, blood, or microsomal suspension both prior to and after the sodium fusion step.

### Sodium Fusion Procedure

All of the chemical procedures are performed in a hood while wearing safty glasses and gloves. A piece of sodium metal approximately 15 to 20 mg is weighed and blotted dry. The sodium cube then is added to a 15 x 120-mm screw-cap culture tube containing the

---

* Research Assistant.

† Research Associate.

Supported by National Institutes of Health Grants CA21820-02 and 2 R01 AM16715-05.

Received from the Department of Anesthesiology, University of Arizona, Tucson, Arizona 85724. Accepted for publication September 10, 1979.

Reprint requests to Dr. Gandolfi.

lyophilized sample or standard. The cap is loosely screwed on the tube, and the tube is placed in a Meker burner. At first the tube is just gently heated (approximately 100 C) to melt the sodium into the lyophilized sample The tube is then placed directly into the flame to produce sodium fumes (bluish vapor, approximately 800 C) at which time the fusion is complete. The tubes are set aside and allowed to cool to room temperature, after which residual sodium metal is destroyed by the addition of 50 μl of anhydrous methanol. Distilled deionized water (2 ml) is then added to each tube, followed by 500 μl of 6 M potassium acetate buffer, pH 6.0, to neutralize the sample. Aliquots (500 μl) of the neutralized samples are mixed with 2 ml of TISAB (Orion Research, Inc) and analyzed using a Corning 110-mV meter equipped with a fluoride ion specific electrode (Orion Research, Inc).

### Calculation of Organic Fluoride

Calibration curves were prepared by plotting millivolt values versus concentration of sodium fluoride standards added. Organic fluoride from samples can be calculated by subtracting the free fluoride in the original sample[7] from the total fluoride content determined by the sodium fusion technique.

### Application of Technique

At various time points following anesthesia, urine samples were obtained from consenting adult patients anesthesized for 2 hours with enflurane (1.8%) or halothane (0.7%). A 200-μl aliquot of urine was treated with 50 μl of 0.1 N NaOH, lyophilized, and processed through the sodium fusion procedure. Urinary free inorganic fluoride was separately determined by a published technique.[7]

## Results

Standards of sodium fluoride in water, buffer, urine, blood or microsomes were processed through the sodium fusion technique and found to produce the same millivolt readings as those generated by addition of the sodium fluoride after the fusion reaction. This indicates there will be no loss of inorganic fluoride generated during the fusion process. In addition, the same millivolt curve was obtained with sodium fluoride standards, regardless of the media. Background interference readings on the fluoride-specific electrode were dependent on the sample aliquot or the nature of the material, but were equivalent to 2 nmoles of fluoride or less. Thus, the sodium fusion procedure for organic fluoride was calculated using sodium fluoride standards for the detection of fluoride ion released following the fusion reaction.

Lyophilized alkaline samples (N = 6) of trifluoroacetate and fenfluramine (0.02 to 410 μmoles) were processed through the sodium fluoride procedure, and their total fluoride content was calculated. Over the entire range of concentration, three fluoride equivalents were detected for each equivalent of either compound processed through the sodium fusion procedure (Fig 1). At a fixed concentration over numerous experiments the same level of fluoride was detected from a trifluoroacetate sample.

When trifluoroacetate was added to phosphate buffer, urine, blood, or microsomal suspensions, the efficiency for decomposition of the compound to free fluoride ion by the sodium fusion technique was less than that occurring with aqueous trifluoroacetate solutions (Table). It should be noted that the efficiency for sodium fusion was dependent on the media and

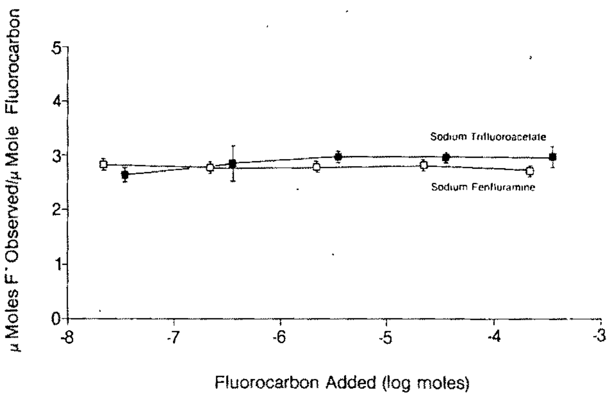


FIG 1. Detection of organic fluoride from various quantities of trifluoroacetate and fenfluramine. Values are means ± standard deviation (N = 5) for trifluoroacetate (■) and fenfluramine (□).

**TABLE 1**

**Efficiency of Organic Fluoride Detection in Various Biologic Samples by Sodium Fusion Technique**

| Trifluoroacetate added to* | Total fluoride detected† |
|---|---|
| | % |
| Water | 98.1 ± 4.5 |
| 0.5 M sodium, phosphate, pH 7.4 | 84.0 ± 5.2 |
| Urine | 48.1 ± 4.5 |
| Blood | 40.5 ± 2.4 |
| Microsomes | 57.3 ± 5.3 |

* Sodium trifluoroacetate (0 to 13.5 μmoles) added to each sample (0.2 ml) and processed through sodium fusion procedure.

† Means ± standard error for multiple determinations and four concentrations.

not the concentration of trifluoroacetate added. Thus, within a determined range of organic fluoride concentration the efficiency for that media can be used to determine the total fluoride detected in the sample.

Urine from consenting adult patients (N = 5) receiving for 2 hours either enflurane (1.8%) or halothane (0.7%) were analyzed for free and organic fluoride levels by the methods discussed (Fig 2). Using predetermined efficiency of detection for organic fluoride from sodium trifluoroacetate in urine, we found that there were millimolar quantities of organic fluoride in the urine of patients after 2 hours of halothane anesthesia. There were only small amounts of inorganic fluoride appearing in the urine of the patients receiving halothane. These values are similar to previously reported[8] urinary organic and inorganic fluoride levels.

Urine from patients receiving enflurane had maximal levels of ionic fluoride at 12 hours after initiation of anesthesia. Since the metabolities of enflurane are unconfirmed, it was assumed organic fluoride metabolites would have the same efficiency of decomposition by sodium fusion as trifluoroacetate in urine. Using this efficiency, we found the urinary organic fluoride in patients receiving enflurane to rapidly increase during anesthesia and remain elevated even at 4 days after anesthesia. The ratio of urinary organic fluoride to inorganic fluoride was identical with that recently reported.[8]

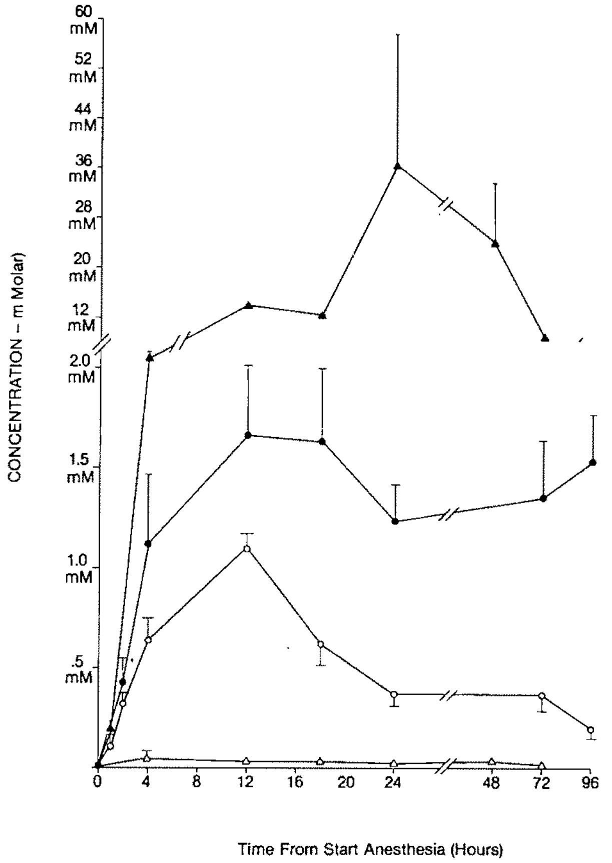


FIG 2. Organic and inorganic fluoride concentrations in urine of patients following anesthesia with enflurane or halothane. Data are the means or means ± standard deviation (N = 5) for patients receiving for 2 hours 0.7% halothane (△ free fluoride, ▲ organic fluoride) or 1.8% enflurane (○ free fluoride, ● organic fluoride).

In separate studies, urine containing either halothane or enflurane gave no response for organic fluoride since the anesthetics are readily removed by lyophilization.

## Discussion

In this study we have shown that the sodium fusion technique is a simple and sensitive method for the determination of organic fluoride in biologic samples. The organic fluoride bond is cleaved by the sodium to produce free fluoride ion which is quantified with a fluoride specific electrode calibrated with sodium fluoride standards. The matrix in which the organofluorine compound is present affects the efficiency of the fusion reaction (Table). The efficiency though is fairly constant over the fluorocarbon quantity generally processed through the sodium fusion reaction. Thus, the absolute organic fluoride present can be calculated in a given biologic sample. The technique is easily reproducible with organofluoride standards yielding little variation in their organic fluoride levels.

Trifluoroacetic acid is noted for the stability of its trifluoromethyl group,[9] yet this technique readily cleaves all three fluorides from the carbon backbone over a wide concentration range in an aqueous medium. Increasing the efficiency of organic fluoride decomposition by sodium fusion in other media will require further experimentation.

The lack of special glassware required for combustion techniques and the ovens required for other methods allows for rapid processing of large numbers of samples (more than 30 samples per hour through the sodium fusion step). This technique readily detects 2 to 10 nmoles of fluoride per milliliter of sample, a level which is much more sensitive than previously reported limits of detection.[3]

### REFERENCES

1. Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 40:536-542, 1974
2. Mazze RI, Hitt BA, Cousins MJ: Effect of enzyme induction with phenobarbital on the *in vivo* and *in vitro* defluorination of isoflurane and methoxyflurane: J Pharmacol Exp Ther 190: 523-529, 1974
3. Holaday DA, Rudofsky S, Treuhaft DS: The metabolic degra-

dation of methoxyflurane in man. Anesthesiology 33:579–593, 1970

4. Venkateswarlu P: Determination of fluorine in biological materials. Methods Biochem Anal 24:102–106, 1977
5. Elving PJ, Ligett WB: Determination of fluorine and other halogens in organic compounds. Ind Eng Chem 14:449–453, 1942
6. Hitt BA, Mazze RI, Cousins MJ: Metabolism of isoflurane in Fisher 344 rats and man. Anesthesiology 40:62–67, 1974
7. Fry BW, Taves DR: Serum fluoride analysis with the fluoride electrode. J Lab Clin Med 75:1020–1025, 1970
8. Sakai T, Takaori M: Biodegradation of halothane, enflurane, and methoxyflurane. Br J Anesth 50:785–791, 1978
9. Rogers IW, Wilson JA: Determination of labile trifluoromethyl compounds with fluoride ion electrode. Anal Biochem 32:31–37, 1969

---

## The Lung as a Filter for Microbubbles

An ultrasonic Doppler device was used noninvasively over the femoral artery of anesthetized dogs to prove that it can detect carefully calibrated microbubbles of 14- to 189-μm diameter when these are infused directly into the aorta. The same technique was then employed to detect bubbles escaping into the arterial system when gas was infused into the venous system either as microbubbles or as a bolus. Results from 18 dogs showed that, under normal conditions, the lungs are a superb filter for bubbles and that any cutoff diameter is less than 22 μm. However, bubbles escaped entrapment when the lungs were severely overloaded with gas (20 ml) or were pretreated with a pulmonary vasodilator (aminophylline). Physiologic parameters showed dramatic changes when bubbles escaped into the arterial system, in comparison with their effect when retained within the lungs. *(Butler BD, Hills BA: The lung as a filter for microbubbles. J Appl Physiol 47:537–543, 1979)*

# CLINICAL reports

# A Possible Hazard with Use of the Ohio Ēthrane Vaporizer

**Levon Capan, MD,* Sivam Ramanathan, MD,* Jack Chalon, MD,† John Barry O'Meara, MD,* and Herman Turndorf, MD‡**

Air-tightness of the anesthesia circuit is essential for proper patient ventilation. Anesthesiologists guard against accidental component disconnections by continuously monitoring breath sounds and chest excursions, and by measuring tidal volume and airway pressures. We recently encountered a circuit interruption that can lead to arterial hypoxia without producing gas leaks detectable by the usual clinical tests.

A patient was anesthetized using a Dräger anesthesia machine (North American Dräger, Telford, PA) fitted with a built-in Dräger respirator. An Ohio Ēthrane vaporizer (outside the circuit), which had been installed permanently on a cabinet-top post, was used to deliver enflurane in a carrier gas mixture of $N_2O$ 2 L/min and oxygen 1 L/min. Inspired oxygen concentration was continuously measured on an Instrumentation Laboratories Analyzer (Lexington, MA). Tidal volume and airway pressure were monitored by appropriate on-line instruments on the expiratory limb of the circuit. An esophageal stethoscope was used to monitor breathsounds. Respiration was mechanically controlled by the Dräger respirator using a tidal volume of 600 ml at a rate of 12 breaths/min at a peak airway pressure of 20 cm $H_2O$. During the course of surgery, the sleeve-ended rubber gas delivery tube was noticed to be disconnected from the metal connector at the vaporizer inlet. There was no detectable gas leak in the circuit and chest expansion and esophageal breath sounds remained unchanged. The tidal volume and peak airway pressure showed decreases of only 50 ml and 3 cm $H_2O$, respectively, and the respirator bellows appeared to be functioning normally. The $F_{IO_2}$ had dropped to 0.24.

The Ohio Ēthrane vaporizer has a unidirectional check-valve at its outlet to minimize pressure changes in the vaporizer during intermittent positive pressure ventilation.[1,2] When discontinuity occurred, inspiratory pressure closed this valve thereby maintaining gas-tightness of the circuit. The resulting effect is similar to closed system ventilation without adding fresh gases.

## Methods

A dog was anesthesized using the same anesthesia system, respirator, and vaporizer (Fig 1). The trachea was intubated with a cuffed tube. Mechanical ventilation was started at a rate of 12/min and a tidal volume of 450 ml, using a fresh gas inflow of 2 L of $N_2O$ and 1 L of oxygen per minute. Inspired humidity,[3] oxygen (Instrumentation Laboratories), and enflurane concentration[4] (calibrated Narkotest analyzer) were measured continuously. Airway pressure was recorded on a polygraph. The oxygen analyzer alarm was set to respond to an $F_{IO_2}$ of 0.2. Breath sounds were continuously monitored by an esophageal stethoscope. After a 30-minute stabilization period, control values for $F_{IO_2}$, $F_{IH_2O}$, $F_{I\text{enflurane}}$, arterial pH, $P_{CO_2}$, and $P_{O_2}$ were obtained. The sleeve-ended rubber gas delivery tube was then detached from the vaporizer inlet

---

* Assistant Professor.

† Professor.

‡ Professor and Chairman.

Received from the Department of Anesthesiology, New York University Medical Center, 560 First Avenue, New York, New York 10016. Accepted for publication August 21, 1979.

Reprint requests to Dr. Ramanathan, Department of Anesthesiology H-623.

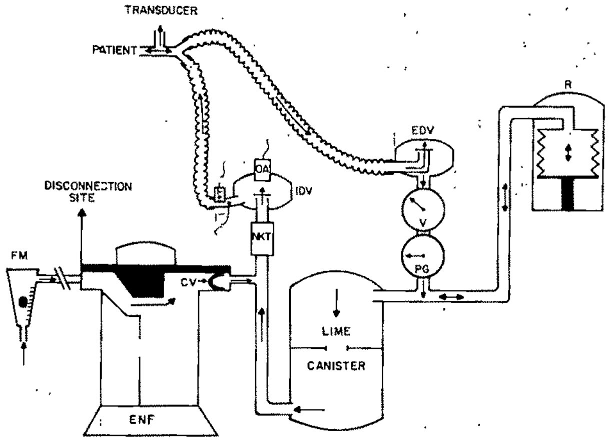


FIG 1. Anesthesia circuit used in the study. FM, Flow meter; ENF, enflurane; CV, check valve; NKT, Narkotest analyzer; IDV, inspiratory dome valve; OA, oxygen analyzer sensor; HS, humidity sensor; IT, inspiratory temperature; EDV, expiratory dome valve; PG, pressure gauge.

and measurements were repeated at 5-minute intervals for 15 minutes. A U-tube water manometer was connected to the vaporizer inlet to note pressure changes during two respiratory cycles. This was disconnected after the measurements, allowing the vaporizer inlet to be open to room air during most of the experiment. This procedure was repeated five times and results were expressed as means ± standard deviation of all measurements. At the end of each experiment, the fresh gas inflow tubing was reattached to the vaporizer inlet and the system allowed to stabilize for 10 minutes. The vaporizer outflow tube was then detached and changes in tidal volume and airway pressure noted.

## Results

Immediately after disconnection, tidal volume decreased to 400 ml and remained at this value for the rest of the experiment. Peak airway pressure (Fig 2, point A) and plateau pressure (Fig 2, point B) decreased 2.8 torr and then remained constant. Baseline airway pressure (Fig 2, point C) fell to −2 torr and the negative deflection (CD) produced by the fall of the respirator bellows decreased from −1.5 torr to −2.5 torr. However, the net pressure change during inspiration (segment CA) and expiration (segment BD) did not change. $F_{IO_2}$ and $Pa_{O_2}$ fell from the control values of 0.34 and 150 torr to 0.125 and 45 torr, respectively (Fig 3). The oxygen analyzer alarm sounded at 6.7 minutes. Arterial $P_{CO_2}$ and pH did not change signif-

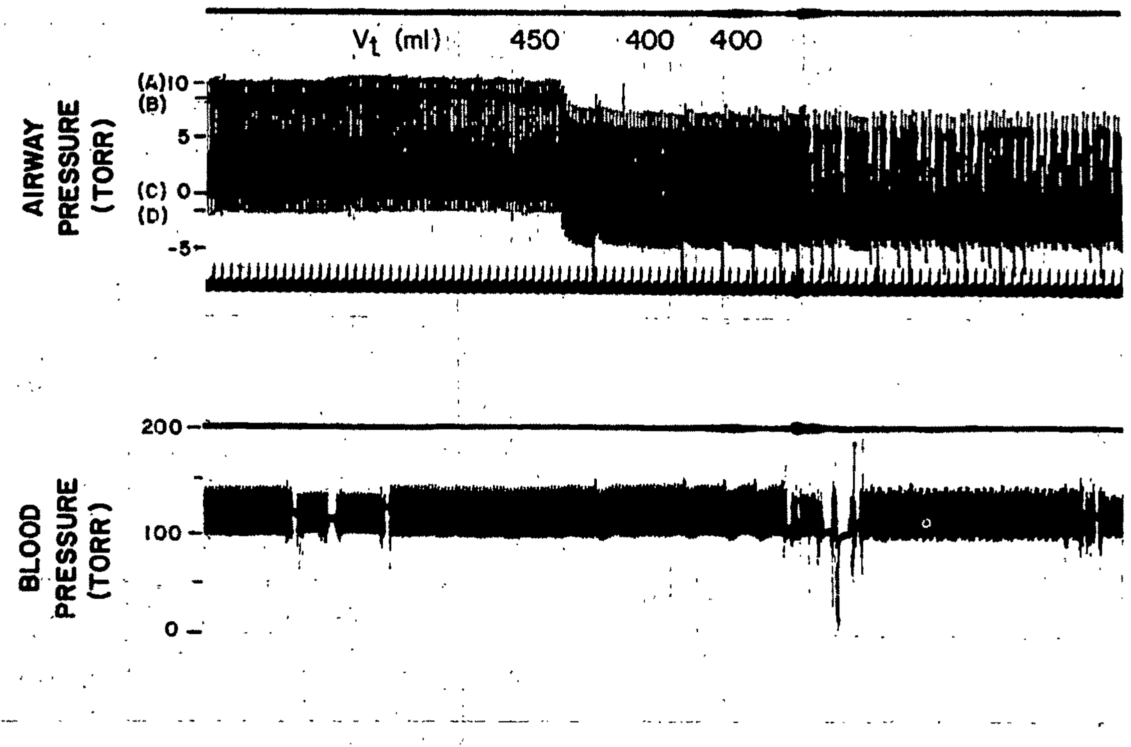


FIG 2. Tidal volume (Vt), airway pressure and blood pressure before and after inflow disconnects. A, Peak airway pressure; B, plateau pressure; C, baseline; D, negative deflection during expiration.

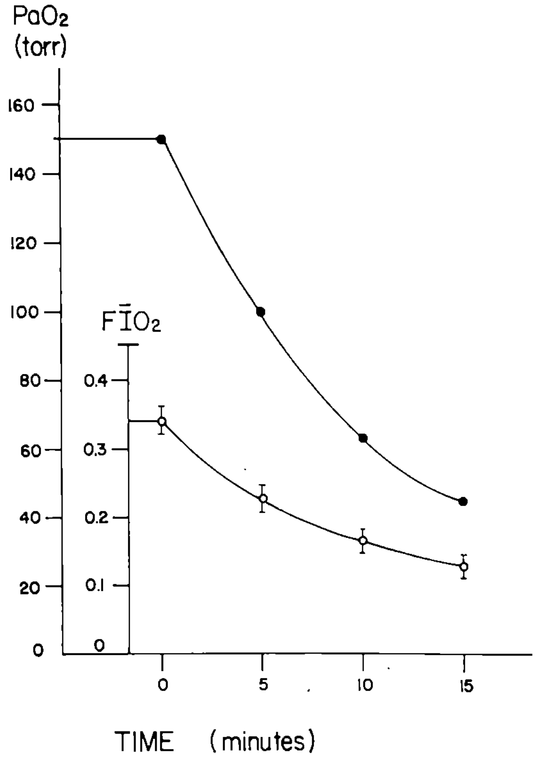


FIG 3. $FI_{O_2}$ and $Pa_{O_2}$ changes after vaporizer inflow disconnection. Results are means of five observations.

**TABLE**

**$FI_{enflurane}$ and $FI_{H_2O}$ Levels before and after Disconnection of Vaporizer Inflow***

| Description | Time in minutes | | | |
|---|---|---|---|---|
| | 0 | 5 | 10 | 15 |
| $FI_{enflurane}$ | 0.011 | 0.007 | 0.005 | 0.004 |
| $FI_{H_2O}$ | 0.01 | 0.021 | 0.023 | 0.026 |

* Results are means of five experiments. For all $FI_{enflurane}$ values SD = ±0.009; for all $FI_{H_2O}$ values SD = ±0.002.

icantly. $FI_{enflurane}$ decreased and $FI_{H_2O}$ increased (Table). We were unable to detect any change in the quality of the esophageal breathsounds. The U-tube manometer registered a negative pressure 1 cm $H_2O$ at the vaporizer inlet. When the vaporizer outflow tube was detached, the tidal volume fell to 200 ml and peak airway pressure dropped to 1 torr immediately.

## Discussion

The check-valve placed at the outlet of the Ohio enflurane vaporizer minimizes the "pumping effect" of the intermittent positive pressure respiration on the anesthetic concentration delivered by the vaporizer.[1, 2] This valve prevents circuit leaks from upstream disconnects. Resultant airway pressure and tidal volume decreases are small and therefore liable to be overlooked. Component separation at the outlet, of course, leads to immediately observable changes in these parameters. We have investigated vaporizers without check-valves (Fluotec and the Dräger "Vapor vaporizer") during clinical anesthesia and found that inflow as well as outflow disconnects produced conspicuous leaks.

Continued patient ventilation through a circle absorber system after fresh gas flow is interrupted results in a rapid fall in $FI_{O_2}$ (Fig 3). This is due to both oxygen consumption by the patient and dilution of oxygen by body nitrogen and by water vapor derived from neutralization of $CO_2$ by soda lime. $Pa_{O_2}$ falls rapidly without significant change in $Pa_{CO_2}$ or pH. In our animal model both $FI_{O_2}$ and $Pa_{O_2}$ fell exponentially to dangerously low levels within 10 minutes. An oxygen analyzer placed in the inspiratory limb will immediately detect a hypoxic gas mixture.

Oxygen removal at a constant rate without replacement will lead to progressive reduction in the volume of a respirator bellows which is inflated only by patient's exhalations and by fresh gas flow during the postexpiratory pause (Airshields Ventimeter ventilator). The contracted bellows may draw the anesthesiologist's attention to the mishap. On the other hand, no noticeable change occurs in the size or position of the bellows after inflow interruption if the respirator bellows returns to its preinspiratory position either by gravity (the Ohio and Dräger respirators) or by mechanical devices (pulley-wire assisted bellows of the Bennet respirator).

The negative deflection (CD) below the baseline (C) in Fig 2 is due to a slight negative pressure in the circuit produced by the rapid descent of the respirator bellows during expiration. When the fresh gas inflow ceases, the volume of gas in the circuit decreases. A given positive pressure change therefore produces less bellows compression and a negative pressure change a slight increase in negative pressure. This phenomenon probably explains the minor decreases in peak and plateau airway pressures as well as in subatmospheric baseline pressure, together with a greater negative deflection (CD) after inflow interruption.

Although the circuit pressure reaches −5 torr during expiration, only a part of the negative pressure could be demonstrated at the disconnect site. This may be due to insufficient pressure gradient across the check valve, which opens only partly. The limited communication with the atmosphere during expiration probably prevents a progressive fall in the baseline pressure of a circuit from which oxygen is removed continuously. The subatmospheric pressure at the vaporizer inlet probably draws a small volume of room air into the system. The volume of air entrained apparently is minimal because of the small magnitude of the aspirating pressure and does not appear to be adequate to avert hypoxia.

In summary, a possible hazard associated with the use of a vaporizer with an outlet check valve is presented. Component separation occurring at the machine side of the vaporizer will produce only minor changes in airway pressure and tidal volume. This accident may escape notice, especially when a respirator with bellows, which does not depend on expired gas for reinflation, is in use. An oxygen analyzer and an electronic circuit pressure monitor with sufficient sensitivity to detect small pressure changes will draw the anesthesiologist's attention to the hypoxia which would otherwise escape immediate notice. Measures that will prevent the occurrence of this mishap include: (1) mounting the vaporizer on the trolley bar of the anesthesia machine, and (2) elimination of a rubber-metal junction at the inlet and outlet of *this* vaporizer.

## REFERENCES

1. Hill DW: Physics Applied to Anesthesia. Second edition, New York, Appleton-Century-Crofts, 1972, pp 222–226
2. Keenan RL: Prevention of increased pressures in anesthetic vaporizers with a unidirectional valve. Anesthesiology 24:732–733, 1963
3. Chalon J, Kao ZL, Dolorico VN, et al: Humidity output of the circle absorber system. Anesthesiology 38:458–465, 1973
4. Lowe HJ, Hagler K: Clinical and laboratory evaluation of an expired anesthetic gas monitor. Anesthesiology 34:378–382, 1971

---

## Adverse Hemodynamic Effects of Plasma Protein Fraction

Paradoxical hypotension during rapid infusion of plasma protein fraction (PPF) has been attributed to vasodilation by bradykinin in PPF. This study employed a canine, controlled right heart bypass preparation to assess changes in systemic vascular resistance and venous capacitance during infusion of PPF and other possibly vasoactive mediators. Plasma protein fraction caused consistent vasodilation, whereas purified human albumin did not. This vasodilation could be ascribed entirely to acetate, present in PPF as a buffer. Infusion of acetate alone in the concentration present in commercial PPF solutions (16.8 meq/L) resulted in a decrease in systemic vascular resistance virtually identical with that observed with infusion of commercial PPF solutions which also contained bradykinin. Acetate is used widely as a buffer in intravenous and dialysate solutions. Its vasoactive properties must be recognized when such solutions are administered to patients with limited capacity to compensate for sudden vasodilation. *(Olinger GH, Werner PH, Bonchek LI, et al: Vasodilator effects of the sodium acetate in pooled protein fraction. Ann Surg 190:305–311, 1979)*

ANESTH ANALG
59: 69–71, 1980

# Persistent Electromechanical Cardiac Arrest following Administration of Cardioplegic and Glucose-Insulin-Potassium Solutions

**Ercument A. Kopman, MD,* and**
**Rebecca C. Ramirez-Inawat, MD†**

Use of a solution containing glucose, insulin, and potassium (GIK), together with a cold cardioplegic solution, to protect the myocardium during aortic cross-clamping has been employed in open heart surgery.[1-4] It has, however, been reported as being associated with hyperkalemia and difficulty in restoring contractility at the conclusion of cardiopulmonary bypass.[5]

We report a prolonged electromechanical cardiac arrest secondary to cold cardioplegia and administration of a GIK solution.

## Case Report

A 65-year-old man weighing 65 kg was admitted to the hospital because of increasing shortness of breath, retrosternal discomfort, and irregular cardiac rhythm. Cardiac catheterization revealed mitral stenosis with good left ventricular function and a normal coronary arterial system. He was receiving maintenance doses of digitalis and guinidine because of atrial fibrillation. He was brought to surgery for mitral valve replacement.

Premedication consisted of morphine sulfate, 10 mg, and scopolamine, 0.4 mg, intramuscularly 1 hour before induction of anesthesia. An arterial cannula, an intravenous line, and a Swan-Ganz catheter were placed to measure hemodynamic variables and for administration of blood and fluids. Before induction of anesthesia, serum electrolyte and blood glucose levels, as well as arterial gas tensions were normal, and arterial pressure was 100/60 torr, pulmonary artery pressure 19 torr, and pulmonary arterial wedge pressure 16 torr. Heart rate ranged between 60–75 beats/min because of the atrial fibrillation. Anesthesia was induced with sodium thiopental, 75 mg, and diazepam, 10 mg, and was then maintained with $N_2O$-$O_2$, 50:50, and morphine, 1.5 mg/kg. Tracheal intubation was facilitated with pancuronium, 10 mg.

All hemodynamic variables remained stable until cardiopulmonary bypass was begun. Priming solutions consisted of 2,000 ml of lactated Ringer's solution and a GIK solution consisting of 80 meq of KCl, 60 units of insulin, and 100 gm of dextrose.

After initiation of cardiopulmonary bypass, body temperature was lowered to 30 C. The pericardial cavity was irrigated with 4 C lactated Ringer's solution for topical cooling during aortic cross-clamping. The ascending aorta then was cross-clamped and 250 ml of cold cardioplegic solution containing 10 meq of KCl (40 meq/L) was infused under pressure into the aortic root. Myocardial temperature was not measured during the procedure. Electromechanical arrest occurred within 50 seconds and the EKG became isoelectric reflecting zero transmembrane potential. Arterial perfusion pressure was maintained above 80 torr. During the first 5 minutes after cardiopulmonary bypass, metaraminol, 1 mg, was administered to raise the perfusion pressure above 60 torr. Sodium nitroprusside was administered to lower the perfusion pressure during the last 10 minutes of cardiopulmonary bypass.

The mitral valve was replaced during a total aortic cross-clamping time of 30 minutes. The aorta was then unclamped and coronary perfusion reestablished. Within 15 minutes core body temperature had reached 37 C. During this 45-minute period, 150 ml of urine were obtained. Despite rewarming, neither electrical nor mechanical activity returned to the heart. Several attempts to pace electrically the left ventricle and the left atrium were unsuccessful. Blood gas tensions were normal. Blood chemistries, however, revealed serum potassium to be 8.5 meq and blood glucose 300 mg/100 ml. Mannitol, 12.5 gm, and furosemide, 60 mg, were given to promote urine flow and potassium excretion. In the hour following the administration of the diuretics, 1,800 ml of urine were excreted. Serum potassium decreased to 3.8 meq. At this time ECG returned to normal. Because of difficulty in terminating cardiopulmonary bypass, an aortic balloon pump was inserted. The endotracheal tube and the aortic balloon pump were removed the next morning.

## Discussion

Cardioplegic solutions are designed to induce rapid cardiac arrest as a means for delaying or reducing ischemic damage to the heart during cessation of coronary blood flow when open heart surgery re-

---

* Associate Professor.

† Fellow in Anesthesiology.

Received from the Department of Anesthesiology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110. Accepted for publication August 27, 1979.

Reprint requests to Dr. Kopman.

quires aortic cross-clamping. Although the composition of currently used solutions varies, the basic principles underlying their use are similar. These solutions are infused into the aorta, proximal to the clamp, for a few minutes immediately following aortic cross-clamping. In the absence of aortic regurgitation, hyperkalemic cardioplegic solutions pass through the coronary arteries where the increased extracellular potassium concentration decreases transmembrane potassium gradient with the immediate and persistent depolarization of myocardial cell membranes. This rapid cardiac arrest, with cessation of myocardial work, prevents depletion of high energy phosphates which are essential for return of normal myocardial function following removal of the aortic clamp and restoration of coronary blood flow.

Another potassium-containing infusate that has been used along with cold cardioplegia in open heart surgery is the GIK solution. Although the results are conflicting,[6, 7] GIK solutions have been used clinically in an attempt to reduce myocardial infarct size,[8] lessen the frequency of ventricular arrhythmias,[9] and limit the mortality during myocardial infarction. Accordingly, GIK solutions have been added to various infusates during open heart surgery, as well as to solutions used to prime extracorporeal oxygenator, assuming that a similar protection may be provided during aortic cross-clamping.

The amounts of potassium in cold cardioplegic and in GIK solutions are variable, changing from one instutition to another. The need for potassium in the range of 20–40 meq/L in cardioplegic solution has been questioned.[5] Several experimental studies have demonstrated no additive effect of potassium in the perfusion solution as long as the solution is cold (about 4 C).[5]

Potassium concentrations in cardioplegic solutions higher than 40 meq/L may cause hyperkalemia and difficulties in reestablishment of normal cardiac function at the end of cardiopulmonary bypass.[5] In our patient, the cause of persistent electromechanical cardiac arrest secondary to hyperkalemia could have been related to inadequate time for either washout of potassium from the myocardial cell or shift of potassium into the cells because of short duration of cardiopulmonary bypass. Whether the GIK, or cardioplegic solutions, or the combination, was responsible cannot be determined.

Our patient probably represents the extreme end of a spectrum (between decreased contractility and electromechanical cardiac arrest) and reacted much more severely than expected for the amount and types of cardioplegic solution or set of solutions. The treatment of hyperkalemia following cardiopulmonary bypass should consist of (1) continuation of cardiopulmonary bypass until electromechanical activity returns to normal; (2) administration of insulin, 10 units, if blood glucose is above 600 mg (in our institution we do not treat hyperglycemia below 600 mg because of spontaneous decrease of blood glucose level); (3) glucose-insulin infusions rapidly reduce the serum potassium level by causing potassium to shift into cells; thus, we usually administer 1 unit of insulin for each 2 gm of glucose given, e.g., 200 to 300 ml of 20% glucose and 20 to 30 units of regular insulin may be administered intravenously over a 30- to 60-minute period; (4) administration of diuretics to promote potassium excretion; (5) calcium may antagonize the cardiac toxicity of hyperkalemia, particularly when hypocalcemia is present; calcium gluconate, 5 to 10 ml of a 10% solution, may thus prove useful when injected over a 2- to 5-minute period; and, (6) sodium bicarbonate causes rapid movement into cells; 45 meq may be injected intravenously over a 3-minute period and repeated after 10 to 15 minutes if ECG abnormalities persist.

Although administration of insulin, diuretics, calcium, and/or bicarbonate may be effective in reducing high serum potassium levels, we prefer to give mannitol, 12.5 gm, and furosemide, 60 mg, assuming that mannitol might also increase contractility by reducing tissue swelling caused by transient hypoxic cardiac arrest.[10] In our patient 1,800 ml of urine were excreted in 1 hour with concomitant reduction of serum potassium and restoration of normal ECG. The amount of potassium in the urine was not determined.

Difficulty in coming off bypass is not an uncommon event. Common causes include (1) prolonged cross-clamp time in the presence of inadequate myocardial protection (pharmacologic); (2) inadequate cooling during bypass; (3) increased coronary vascular resistance due to cell swelling; (4) prolonged bypass time; (5) previously inadequate myocardial contractility. In our patient, electromechanical cardiac arrest can probably be explained by the high serum potassium level. The poor contractility necessitating mechanical assistance, on the other hand, was probably related to one of the other factors mentioned above.

Although potassium may play an active role as a metabolic inhibitor, it may not be essential in patients in whom aortic cross-clamping lasts less than 45 minutes. It has been suggested that a significant factor in providing myocardial protection is the ability to produce and maintain a cold myocardium during cross-clamping, rather than the composition of the protective solutions.[5] The uniqueness of our patient was the short duration of cardiopulmonary bypass, one large dose of GIK, and use of cardioplegic solutions. We now use 40 meq in GIK solutions and 20 meq/L in cardioplegic solutions. This case suggests that for short procedures requiring short arrest time (mitral or aortic valve replacement, single coronary bypass) avoidance of high potassium concentrations in GIK and cardioplegic solutions may prevent this problem.

## REFERENCES

1. Mundth ED, Goel IP, Morgan RJ, et al: Effect of potassium cardioplegia and hypothermia on left ventricular function in hypertrophied and non-hypertrophied hearts. Surg Forum 26: 257–258, 1975
2. Goldstein SM, Nelson RL, McConnell DH, et al: Cardiac arrest after aortic cross-clamping: effects of conventional vs pharmacologic arrest on myocardial supply/demand balance. Surg Forum 26:271–273, 1975
3. Tyers GFO, Manley NJ, Williams EH, et al: Preliminary clinical experience with isotonic hypothermic potassium-induced arrest. J Thorac Cardiovasc Surg 74:674–680, 1977
4. Adams PX, Cunningham JN Jr, Brazier J, et al: Technique and experience using potassium cardioplegia during myocardial revascularization for preinfarction angina. Surgery 83:12–19, 1978
5. Tucker WY, Ellis RJ, Mangano DT, et al: Questionable importance of high potassium concentrations in cardioplegic solutions. J Thorac Cardiovasc Surg 77:183–190, 1979
6. Stanley AW, Moraski RE, Russell RO Jr: Effects of glucose-insulin-potassium on myocardial substrate availability and utilization in stable coronary artery disease. Am J Cardiol 36:929–937, 1975
7. Opie LH, Owen P: Effect of glucose-insulin-potassium infusions on arteriovenous differences of glucose and of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction. Am J Cardiol 38:310–321, 1976
8. Maroko PR, Libby P, Sobel BE, et al: Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. Circulation 45:1160–1175, 1972
9. Regan TJ. Harman MA, Lehan PH, et al: Ventricular arrhythmias and $K^+$ transfer during myocardial ischemia and intervention with procaine amide, insulin or glucose solution. J Clin Invest 46 1657–1668, 1967
10. Brachfeld N: Metabolic evaluation of agents designed to protect the ischemic myocardium and to reduce infarct size. Am J Cardiol 37:528–532, 1976

ANESTH ANALG
59: 72-73, 1980

# Spinal Subdural Hematoma Associated with Attempted Epidural Anesthesia and Subsequent Continuous Spinal Anesthesia

**Fred S. Greensite, MD,* and**
**Jordan Katz, MD†**

Spinal subdural hematoma with resulting cauda equina syndrome has not been previously reported in association with regional anesthesia in patients without coagulopathies or spinal tumors. We report such an event following attempted epidural anesthesia and subsequent continuous spinal anesthesia.

## Case Report

A 68-year-old white man was admitted for right total knee replacement. Past medical history was remarkable only for degenerative joint disease. He had been taking aspirin and other anti-inflammatory drugs until a left total knee replacement was performed 5 months prior to admission after which his only medication was acetaminophen, 650 mg three times daily. Review of systems and physical examination were noncontributory. Preoperative white blood count was 5,300 with a normal differential. From examination of a blood smear platelet numbers were described as adequate by the laboratory. Prothrombin time was 11.2 seconds (normal 11.3 seconds) and partial thromboplastin time 30.5 seconds (normal 30.5 seconds). An Ivy bleeding time done at the time of his prior knee surgery was 4 minutes 13 seconds (normal 2 to 10 minutes).

A continuous epidural anesthetic was planned. On arrival in the operating room the patient was placed in the right lateral decubitis position. A 16-gauge Tuohy needle was advanced in the L2-3 interspace using a loss of resistance technique. Dark gross blood was noted to drip from the needle which was immediately removed and reinserted into the L3-4 interspace. Loss of resistance was not encountered until the dura was punctured with free return of clear cerebrospinal fluid. A 20-gauge Portex epidural catheter was advanced with ease cephalad 2 cm into the subarachnoid space. There were no paresthesias nor any unusual pain at any time during the procedure. Administration of a continuous spinal anesthetic proceeded uneventfully using 1% tetracaine in 10% dextrose in water. Reinjection was required once during surgery; aspiration of spinal fluid through the catheter was not attempted prior to reinjection. The catheter was removed intact and without difficulty at the end of the operation. The patient regained motion in his legs and was returned to his ward after 2 hours in the recovery room. Postoperative medications included aspirin, 650 mg twice daily; the first dose was administered 4 hours postoperatively.

Twenty-four hours postoperatively the patient was without complaints, moving his legs and voiding without difficulty. Approximately 36 hours postoperatively the onset of urinary incontinence and sacral paresthesias occurred which progressed over the next 12 hours to paraplegia. An emergency myelogram was performed. Attempted dural puncture at L3-4 yielded gross blood and the study was accomplished using a cervical approach. It demonstrated extramedullary block at the level of L1, with a presumptive diagnosis of epidural hematoma. At laminectomy no extradural hematoma was seen but incision of the dura revealed a large amount of blood in the subdural space with clot extending from L2 to T12. Oozing blood was noted but no specific bleeding point identified. Apart from unusually large epidural veins noted by the neurosurgeon there were no vascular abnormalities or tumors. The clot was evacuated. Postoperatively prothrombin and partial thromboplastin times as well as platelet counts on peripheral smears were within normal limits.

Five months after laminectomy the patient remained paraplegic.

## Discussion

Large series such as those of Dripps and Vandam[1] and of Phillips et al[2] have established the rarity of central nervous system sequellae following subarachnoid anesthesia. The incidence appears to be less than 1:10,000 using modern techniques and precautions. In the above-combined series of approximately 20,000 spinal anesthetics there were no cases of cauda equina syndrome or arachnoiditis despite an incidence of 3% bloody taps in the series of Phillips et al. Continuous spinal anesthesia constitutes a small percentage of subarachnoid anesthesia although it has been recommended as the anesthetic of choice in seriously ill

---

* Resident, Department of Anesthesiology, University of California, San Diego.

† Professor and Vice Chairman, Department of Anesthesiology, University of California, San Diego; Chief, Anesthesia Service, VA Medical Center, San Diego.

Received from Anesthesiology Service, VA Medical Center, La Jolla, California 92161. Accepted for publication September 5, 1979.

Reprint requests to Dr. Katz, Anesthesiology Service, VA Medical Center, 3350 La Jolla Village Dr, San Diego CA 92161.

patients for lower abdominal or leg operations.[3] In a series of 600 continuous spinal anesthetics Brown[4] reported no permanent neurologic sequellae. Permanent neurologic deficits following epidural anesthesia have an incidence of approximately 1:11,000.[5]

Occasional reports of epidural hematoma following epidural or spinal anesthesia primarily in patients receiving anticoagulation therapy[6] have caused these forms of anesthesia to be considered contraindicated in the presence of clotting abnormalities.

In contrast to epidural hematoma, spinal subdural hematoma is extraordinarily unusual. There are about 20 case reports in the world literature, mostly following minor trauma or in patients with clotting abnormalities undergoing diagnostic lumbar puncture.[5, 7, 8] We have found only three instances associated with spinal or epidural anesthesia. In one case the patient had a blood dyscrasia.[9] In another case a vascular tumor and spinal bifida in the lumbar spinal canal were present.[5] The third patient had onset of neurologic symptoms 18 months after anesthesia making a relationship between lumbar puncture and subdural hematoma questionable.[10]

Unlike epidural bleeding the source of spinal subdural bleeding is unclear. Edelson et al[7] considered the possible sources of spinal subdural bleeding in patients with thrombocytopenia. They note that blood vessels are not apparent on inspection of the spinal subdural surfaces and that bridging subdural veins present over the brain are not observed in the spinal cord. At the level of the cauda equina the only vessels that are 1 mm or larger in diameter are the artery and vein of Adamkiewicz which run longitudinally and lie laterally in the subdural space.

Evidence that the postoperative aspirin might have been a contributory factor in the hematoma formation is suggestive but circumstantial. Aspirin decreases platelet adhesiveness through inhibition of release of platelet adenine diphosphate,[11] a defect which lasts for the lifetime of the exposed platelet. It has been shown that preoperative aspirin therapy can be associated with markedly excessive blood loss in the perioperative period[12] and there have been admonishments against preoperative use of aspirin for this reason.[13, 14] Sahud and Cohen[15] showed that mean Ivy bleeding time in normal patients increased by an average of 50% 2 hours after a single oral dose of 600 mg of aspirin.

Using a technique to quantitate the amount of bleeding during bleeding time assessments, Sutor et al[16] showed that within 70 minutes of ingesting 650 mg of aspirin 75% of normal subjects lost at least 4 times more blood than they did prior to ingestion of aspirin. Finally, Locke et al[17] have reported a case of spontaneous acute spinal epidural hematoma unassociated with trauma, conventional anticoagulant therapy, coagulopathy, or vascular abnormalities; they ascribe this case to the ingestion of two doses of "two tablets of aspirin."

The cause for the subdural hematoma in this patient is unclear. It is possible that aspirin therapy in the immediate postoperative period was instrumental in either formation or expansion of the hematoma.

## REFERENCES

1. Dripps RD, Vandam LD: Long term follow-up of patients who received 10,098 spinal anesthetics. JAMA 156:1486-1491, 1954
2. Phillips OC, Ebner H, Nelson AT, et al: Neurologic complications following spinal anesthesia with lidocaine. Anesthesiology 30:284-289, 1969
3. Underwood RJ: Continuous spinal anesthesia in physical status group IV patients. Anesth Analg 47:18-24, 1968
4. Brown S: Fractional segmental spinal anesthesia in poor risk surgical patients: report of 600 cases. Anesthesiology 13: 416-428, 1952
5. Usubiaga JE: Neurological complications following epidural anesthesia. Int Anesthesiol Clin 13: 2-3, 1975
6. De Angelis J: Hazards of subdural and epidural anesthesia during anticoagulant therapy: a case report and review. Anesth Analg 51:676-679, 1972
7. Edelson RN, Chernik NL, Posner JB: Spinal subdural hematomas complicating lumbar puncture—occurrence in thrombocytopenic patients. Arch Neurol 31:134-137, 1974
8. Sokoloff J, Coel MN, Ignelzi RJ: Spinal subdural hematoma. Radiology 120:116, 1976
9. Bonica JJ: The Management of Pain. Philadelphia, Lea & Febiger, 1953 (as quoted in Int Anesthesiol Clin 13:39, 1975)
10. Carrea RME, Giardo M, Eurnekian A: Hematoma cronico epidural y subdural sepinal. Medicina 14:379-392, 1954 (as quoted in Arch Neurol 31:134-147, 1974)
11. Rossi, EC, Green D: Symposium on hemorrhagic disorders. Med Clin North Am 56:40, 1972
12. Davies DW, Steward DJ: Unexpected excessive bleeding during operation: rule of acetylsalicylic acid. Can Anaesth Soc J 24: 452-458, 1977
13. Editorial: Aspirin and bleeding. JAMA 218:89, 1971
14. Editorial: The platelet acquires a personality. N. Engl. J. Med. 280:501, 1969
15. Sahud MA, Cohen RJ: Aspirin-induced prolongation of the Ivy bleeding time. Calif Med 115:10-13, 1971
16. Sutor AH, Bowie EJW, Owen CA: Effect of aspirin, sodium salicylate, and acetaminophenon bleeding. Mayo Clinic Proc 46:178-181, 1971
17. Locke GE, Giorgio AJ, Biggers SL, et al: Acute spinal epidural hematoma secondary to aspirin-induced prolonged bleeding. Surg Neurol 5:292-296, 1976

ANESTH ANALG
59: 74-76, 1980

# Intra-aortic Balloon Counterpulsation for Right Heart Failure

**Ercument A. Kopman, MD,* and Rebecca C. Ramirez-Inawat, MD†**

Intra-aortic balloon counterpulsation (IBC) has been used for several years for the treatment of left ventricular failure after myocardial infarction and in open heart surgery[1, 2] when mechanical support for the cardiovascular system is needed. The beneficial effect of IBC is believed to be due to improvement of left ventricular performance, since it decreases left ventricular afterload and preload and, consequently, left ventricular myocardial oxygen consumption[3, 4] while increasing coronary artery blood flow.

We report the use of IBC in a patient who developed right ventricular failure, as reflected by a high central venous pressure (CVP), following cardiopulmonary bypass, with significant improvement of right ventricular performance.

## Case Report

A 62-year-old man was hospitalized because of chest pain relieved by nitroglycerin. Coronary cineangiography revealed 90% stenosis in the proximal left anterior descending coronary artery and 80% stenosis of the right coronary. Hemodynamic studies and cineangiography showed normal right ventricular function with a moderately elevated left ventricular end-diastolic pressure (12 mm Hg). Laboratory data, including blood counts, hemoglobin, electrolytes, ECG, and serum enzymes, were normal. He was scheduled for a double coronary bypass graft. Premedication consisted of morphine, 10 mg, and scopolamine, 0.5 mg. Prior to induction of anesthesia, the right radial artery was cannulated for blood sampling and monitoring of blood pressure and a #7 French balloon-tipped triple-lumen catheter was introduced via the internal jugular vein into the pulmonary artery for hemodynamic measurements.

Anesthesia was induced with thiopental, 100 mg, and then maintained with $N_2O$-$O_2$, 50:50, pancuronium, 0.1 mg/kg, and morphine. 1.5 mg/kg.

Hemodynamic measurements before cardiopulmonary bypass were: blood pressure 130/70 torr; mean CVP 3 torr; mean pulmonary arterial pressure 19 torr; and mean pulmonary capillary wedge pressure (PCWP) 8 torr.

The anesthetic course was uneventful, and vital signs were stable until cardiopulmonary bypass was begun. After cross-clamping of the aorta a cardioplegic solution was injected into the aortic root and double coronary bypass grafts were performed under moderate hypothermia (28 C). During the aortic cross-clamping, the pericardial cavity was irrigated with cold lactated Ringers solution (4 C) and perfusion pressure was kept between 70 to 90 torr. After rewarming to 37 C, several attempts were made to discontinue cardiopulmonary bypass. They were unsuccessful as evidenced by high CVP (20 torr), low PCWP (6 torr), and low systolic and diastolic arterial pressures (75/40 torr). Despite inotropic support, there was no improvement in right ventricular function as reflected by a continuing high CVP. At this time, blood gas tensions, serum electrolytes, and ECG were normal.

In order to increase diastolic pressure, an intraaortic balloon pump was inserted. Within 10 minutes after insertion of the balloon, CVP decreased to 10 torr and there was a satisfactory augmentation of aortic diastolic pressure. Cardiopulmonary bypass could then be discontinued. To test the effect of the counterpulsation on right ventricular performance, and to eliminate the possibility of a spontaneous improvement, the balloon pump was temporarily turned on and off three times. Each time it was off, CVP rose gradually with a concomitant decline in systemic arterial pressure (Figure).

The patient was ventilated overnight and the ventilator and balloon pump discontinued the next morning. Subsequent progress was satisfactory.

## Discussion

Mechanical circulatory support by ICB provides at least temporary hemodynamic improvement in patients with cardiogenic shock complicating acute myocardial infarction. Its value is based on the principle of reducing myocardial oxygen demand[3, 4] and increasing coronary blood flow,[5-7] while decreasing afterload and preload,[4] thus providing support of both the coronary and systemic circulations. Another application of the IBC is provision of temporary mechanical assistance at the termination of cardiopulmonary bypass.[1, 2] Occasionally, discontinuation of extracorporeal circulation is impossible because of inadequate left ventricular performance. The occurrence of right ventricular failure, however, in patients without chronic pulmonary hypertension is rare.

In our patient, the mechanism responsible for the isolated right ventricular failure is not clear. It is

---

* Associate Professor.

† Fellow in Anesthesiology.

Received from the Department of Anesthesiology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110. Accepted for publication September 10, 1979.

Reprint requests to Dr. Kopman.

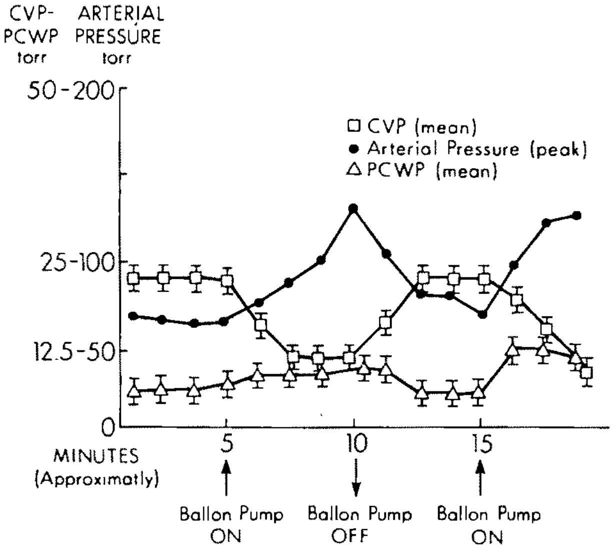


FIGURE. Hemodynamic changes with and without intra-aortic balloon counterpulsation. CVP, Central venous pressure; PCWP, pulmonary capillary wedge pressure.

possible that, because of the differences in resistance in the individual coronary arterial systems, the cardioplegic solution bypassed an ischemic zone of the myocardium. Thus, a portion of the right ventricle could have remained unprotected during aortic cross-clamping.

Also, because of the anatomic location of the right ventricle, topical cooling might have been inadequate.

Although myocardial oxygen consumption is minimal during aortic cross-clamping, high energy phosphate might have been depleted in poorly protected areas of the myocardium, resulting in impaired contractility. As a result of this temporary dysfunction, cessation of cardiopulmonary bypass can be difficult or impossible, necessitating inotropic and/or mechanical assistance.

The hemodynamic consequences of right ventricular failure include an increased end-diastolic pressure in the right ventricle or an increased CVP with low or normal left ventricular end-diastolic pressure and PCWP. The adverse hemodynamic effects of high end-diastolic pressure and volume are 2-fold: (1) increased oxygen demand because of the LaPlace relationship; and (2) reduction in coronary blood flow to the endocardium because of decrease in the endoepicardial (transmural) pressure gradient.

Under these circumstances, since little blood is being pumped to the left side of the heart because of the right ventricular failure at the time of coming off bypass, left ventricular output is impaired, although the left side of the heart itself is not in failure (as evidenced in our patient by a normal PCWP). The beneficial effect of counterpulsation in right ventricular failure is probably due to increased coronary perfusion pressure and, consequently, an increase in blood flow through poorly contracting areas of the right ventricle. Once right ventricular perfusion is improved, contractile power should be restored and the end-diastolic pressure should diminish. Decrease in end-diastolic pressure would increase the transmural pressure gradient with further improvement in contractility.[8, 9]‡

Conflicting results have been reported concerning the alteration of coronary perfusion during counterpulsation. Some investigators[10–12] have failed to demonstrate conclusively that the favorable effects of balloon pumping can be attributed to an increase in collateral coronary flow. However, augmentation of regional coronary blood flow by counterpulsation (documented with the use of radionuclide-labeled microspheres) has been reported.[7] It has been suggested that counterpulsation can effectively augment regional blood flow and help in reperfusion of the regional myocardium,[7] with a concomitant improvement in cardiac function.[11]

Nevertheless, deterioration of the right ventricular performance when counterpulsation was stopped strongly suggests that redistribution of regional coronary flow was improved during balloon pumping in our patient. This report suggests another use for intra-aortic counterpulsation, namely, in right ventricular failure following cardiopulmonary bypass.

## REFERENCES

1. Bergman D, Parodi EN, Edie RN, et al: Intraoperative unidirectional intra-aortic balloon pumping in the management of left ventricular power failure. J Thorac Cardiovasc Surg 70:1010–1023, 1975
2. Buckley MJ, Craver JM, Gold HK, et al: Intra-aortic balloon pump assist for cardiogenic shock after cardiopulmonary bypass. Circulation 47, 48 (Suppl 3):90–94, 1973
3. LeFemine AA, Low HBC, Cohen ML, et al: Assisted circulation. III. Effect of synchronized arterial counterpulsation on myocardial oxygen consumption and coronary flow. Am. Heart J 64:789–795, 1962
4. Spotnitz HM, Covell JW, Ross J, et al: Left ventricular mechanics and oxygen consumption during arterial counterpulsation. Am J Physiol 217:1352–1358, 1969
5. Jacobey JA, Taylor WM, Smith GT, et al: A new therapeutic approach to acute coronary occlusion. II. Opening dormant coronary collateral channels by counterpulsation. Am J Cardiol 11:218–227, 1963
6. Sugg WL, Martin LF, Webb WR, et al: Influence of counterpulsation on aortic right and left coronary blood flow following

---

‡ Nichols AB, Pohost GM, Gold HK, et al: Assessment of left ventricular function on-and-off intra-aortic balloon pump support by gated cardiac blood pool scanning (abstract). Circulation 55,56(Suppl 111):132, 1977.

ligation of the left circumflex coronary artery. J Thorac Cardiovasc Surg 59:345-351, 1970

7. Gill CC, Wechsler AS, Newman GE, et al: Augmentation and redistribution of myocardial blood flow during acute ischemia by intra-aortic baloon pumping. Ann Thorac Surg 16:445-453, 1973
7. Steele P, Jenkins M, Battock D, et al: Isosorbide dinitrate and intra-aortic balloon pumping in preinfarctional angina: effects on central circulatory dynamics. Chest 69:712-717, 1976
9. Watson JT, Fixler DE, Platt MR, et al: The influence of combined intra-aortic balloon counterpulsation and hyperosmotic mannitol on regional myocardial blood flow in ischemic myocardium in the dog. Circ Res 38:506-513, 1976
10. Kerber RE, Marcus ML, Ehrhardt J, et al: Effect of intra-aortic balloon counterpulsation on the motion and perfusion of acutely ischemic myocardium: an experimental echocardiographic study. Circulation 53:853-859, 1976
11. Reneman RS, Jageneau AHM, Schaper WKA, et al: Influence of counterpulsation on collateral circulation after acute occlusion of the left anterior descending coronary artery in dogs. Cardiovas Res 6:45-53, 1972
12. Saini VK, Hood WB Jr, Hechtman HB, et al: Nutrient myocardial ischemia: effects of intra-aortic balloon counterpulsation and coronary reperfusion. Circulation 52:1086-1090, 1975

---

## Acute Pulmonary Complications of Molar Pregnancy

Twelve of 128 patients (10.7%) receiving primary treatment for molar pregnancy after uterine evacuation developed self-limited, acute pulmonary complications characterized by tachycardia, tachypnea, and hypoxemia. The respiratory syndrome occurred primarily in patients with uteruses large for dates and greater in size than 16 weeks gestation. Multiple contributing factors were identified; these include trophoblastic deportation, hyperthyroidism, fluid overload, dilution anemia, and preeclampsia. Although the final outcome of the respiratory syndrome was uniformly benign in this group, deaths have been reported. Supportive measures plus correction of contributing factors are suggested as the rationale for theory. *(Twiggs LB, Morrow CP, Schlaerth JB: Acute pulmonary complications of molar pregnancy. Am J Obstet Gynecol 135:189–194, 1979)*

ANESTH ANALG
59: 77-78, 1980

# Severe Circulatory Shock following Protamine (An Anaphylactic Reaction)

**S. S. Moorthy, MD,* William Pond, MD,† and Randall G. Rowland, MD‡**

Administration of protamine intravenously to neutralize the anticoagulant effects of heparin may be associated with hypotension, particularly when the rate of infusion is rapid. We recently observed profound hypotension accompanied by tachycardia and generalized skin erythema following the slow intravenous administration of 20 mg of protamine sulfate to a diabetic patient on protamine zinc insulin. The abrupt onset and the resistance of hypotension to therapy suggested an anaphylactic response to protamine.

## Case Report

A 26-year-old, 50 kg, woman with a 7-year history of multiple sclerosis and insulin-dependent diabetes for 5 years was admitted for removal of right renal calculi. Her diabetes was controlled with 25 units of protamine zinc insulin daily. The patient had no allergies. The physical examination was unremarkable except for flexor contractures of both lower extremities secondary to multiple sclerosis. Hemoglobin and serum electrolyte and creatinine levels were normal. Preanesthetic medication consisted of intramuscular morphine, 6 mg, glycopyrrolate, 0.2 mg, and 10 units of protamine zinc insulin on the morning of surgery.

Anesthesia was induced with 250 mg of thiamylal. After 5 mg of pancuronium, the trachea was intubated and the patient placed in the right lateral flank position. Anesthesia was maintained with fentanyl, nitrous oxide, and oxygen; pancuronium was used for muscle relaxation. Before clamping the renal vessels for nephrolithotomy, heparin, 5,000 units, was administered intravenously. After removal of the renal calculi and placement of a nephrostomy tube, the kidney was closed. At this time estimated blood loss was 500 ml and the fluids administered included 1,000 ml of whole blood, 1,500 ml of balanced salt solution, and 500 ml of reconstituted plasma. Because of persistent bleeding from the nephrostomy tube, 20 mg of protamine was given intravenously over a 5-minute period. At the completion of protamine infusion the systolic blood pressure decreased from 100 to 40 torr and the heart rate increased from 50 to 140 beats/min. In addition generalized skin erythema was present. The kidney rest was lowered and the patient was placed in a 10 to 15° head-down position, controlled ventilation was continued, and oxygen was substituted for nitrous oxide. Pharmacologic measures to raise the blood pressure included 6 mg of phenylephrine (repeated doses of 1 mg), 1.5 mg of epinephrine (0.5 mg each dose), and 200 mg of hydrocortisone. Diphenhydramine hydrochloride (Benadryl), 50 mg, was also administered intravenously. An infusion of norepinephrine was given. Entertaining the possibility of a septic shock, 1 g of methylprednisolone was given intravenously. Plasmanate, 1,000 ml, was administered over a 20-minute period. Arterial blood gas tensions, pH, and glucose levels during the period of hypotension were $Pa_{O_2}$ 71 torr, $Pa_{CO_2}$ 51 torr, pH 7.39, and 166 mg/100 ml, respectively. Systolic blood pressure gradually increased to 60 torr over a 20-minute period. Blood pressure continued to increase without further pharmacologic support and the heart rate gradually decreased to normal levels (Figure). The remainder of the operative and postoperative course were uneventful with the patient's diabetes controlled with lente insulin.

Serum IgE levels measured 1 month postoperatively were 337 units/ml (normal 10 to 168 units/ml).

## Discussion

This patient manifested profound and resistant hypotension plus tachycardia and a generalized erythematous rash following the slow administration of a small dose of protamine. The characteristics of this response suggest an anaphylactic reaction. We speculate that this patient was sensitized to protamine secondary to treatment of diabetes mellitus with protamine zinc insulin. The protamine content in 25 units of protamine zinc insulin is about 0.7 mg. The administration of 20 mg intravenously represented a massive dose relative to that present in the insulin dose.

Intravenous administration of large doses of protamine to reverse heparin has been associated with hypotension and bradycardia. Myocardial depression[1] and peripheral vasodilation[2] are alleged to be responsible for the hypotensive effect. A minimal effective dose and slow injection has been recommended to mitigate the hypotensive effect. Slow injection of protamine associated with profound hypotension and tachycardia and skin erythema as ob-

---

* Assistant Professor, Department of Anesthesia.

† Resident, Department of Anesthesia.

‡ Assistant Professor, Department of Urology.

Received from the Departments of Anesthesia and Virology, Indiana University School of Medicine, Indianapolis, Indiana 46223. Accepted for publication September 12, 1979.

Reprint requests to Dr. Moorthy.

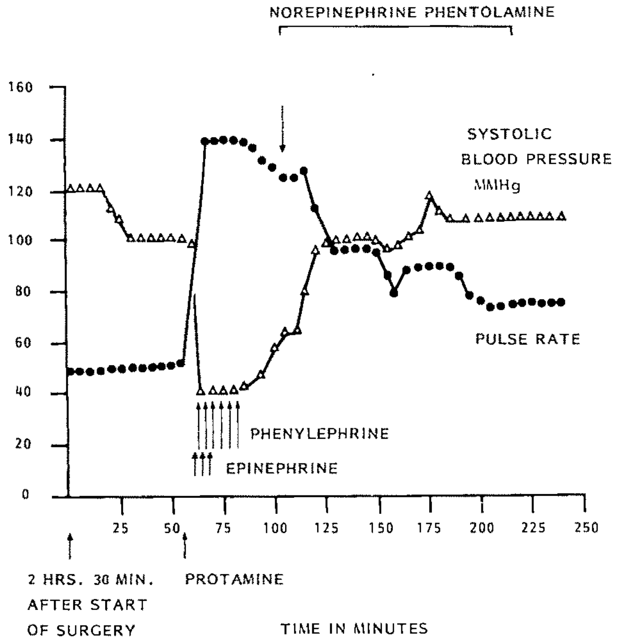


FIGURE. Systolic blood pressure and pulse rate changes following protamine, 20 mg IV. Note the absence of response to continuous administration of vasopressors—phenylephrine (1 mg six times) and epinephrine (0.5 mg three times) and norepinephrine infusion.

served in our patient do not fit into the commonly described responses to protamine. The combination of the hypotensive response plus elevated IgE levels suggests an anaphylactic response to protamine with the release of mediator substances such as histamine. IgE is the reaginic antibody present in increased amounts in individuals with immediate hypersensitivity (type I allergy). With an antigen challenge, IgE molecules attached to the surface of mast cells react with the antigen releasing histamine and other vasoactive amines from the mast cells.[3,4] These substances produce the symptoms and signs of anaphylaxis.

We conclude that protamine should be administered cautiously to patients receiving protamine zinc insulin.

## ACKNOWLEDGMENTS

We thank Dr Robert Stoelting, Professor and Chairman of the Department of Anesthesia, for suggestions with regard to the manuscript. We also thank Ms Linda Hicks for secretarial help.

## REFERENCES

1. Goldman BS, Joison J, Austen WG: Cardiovascular effects of protamine sulfate. Ann Thorac Surg 7:459–471, 1969.
2. Gourin A, Streisand RL, Stuckey JH: Total cardiopulmonary bypass, myocardial contractility, and the administration of protamine sulfate. J Thorac Cardiovasc Surg 61:160–166, 1971
3. Morrow DH, Luther RR: Anaphylaxis: etiology and guidelines for management. Anesth Analg 55:493–499, 1976
4. Watkins J: Anaphylactoid reactions to IV substances. Br J Anaesth 51:51–60, 1979

ANESTH ANALG
59: 79-80, 1980

# Coma and Abnormal Neurologic Signs following Premedication

Stanley I. Samuels, MB, BCh,* and
Edward Washington, MD†

A case is reported in which coma and meningismus were noted as part of a central anticholinergic syndrome probably caused by scopolamine given preoperatively. This led to extensive diagnostic studies and postponement of surgery. Menignismus has not previously been reported to be a sign of the central anticholinergic syndrome. Hyperreflexia, positive Babinski sign and coma, previously described as signs of the anticholinergic syndrome,[1] were observed in our patient. When these signs are noted together with meningismus, they can lead to a mistaken diagnosis of a cerebrovascular accident.

## Case Report

A 52-year-old, 55 kg, white woman was scheduled for a pancreatoduodenectomy for carcinoma of the common bile duct. Past medical history was unremarkable except for an exploratory laparotomy in another hospital 10 days prior to admission. The patient stated that there were no anesthetic or surgical complications from this procedure. At that time the diagnosis of adenocarcinoma of the common bile duct was made and she was referred to Stanford University Hospital for definitive surgery. Clinical examination was negative and laboratory data showed abnormal liver function, specifically lowered serum protein levels, i.e., total protein 4.5 g/100 ml (normal 6 to 8), albumin 2.9 g/100 ml (normal 3.5 to 5.5). She had no history of drug allergies and her only medication was meperidine, 75 mg IM every 2 to 3 hours for pain. The last dose of meperidine was administered 8 hours prior to premedication for surgery. Following this injection the patient was awake, alert, and comfortable.

Premedication consisted of meperidine, 100 mg, hydroxyzine, 50 mg, and scopolamine, 0.4 mg, intramuscularly. On arrival in the operating room the patient was deeply comatose and unresponsive to verbal commands or to painful stimuli. Respirations were 16 breaths/min and regular, pulse 100 beats/min, and systolic blood pressure 120 torr. Neurologic examination revealed the pupils to be centrally fixed and 3 mm dilated; the optic fundi showed no abnormalities. Deep tendon reflexes were hyperactive, an extensor plantar response was noted bilaterally (Babinski reflex) and there was marked nuchal rigidity.

The presumptive diagnosis was either a cerebrovascular accident or drug-induced coma. It was believed that prior to any elaborate medical evaluation, an attempt should be made to antagonize or reverse the premedicant drugs. Consequently, naloxone, 0.8 mg, was administered in divided doses which produced little change in the level of consciousness. The meningismus and Babinski and increased deep tendon reflexes persisted. Physostigmine, 1 mg, was given intravenously with no effect. It was then decided to proceed with a variety of laboratory tests in an attempt to discover the cause of coma. These included arterial blood gas, blood glucose, and serum electrolyte determinations. A spinal tap was performed for analysis of cerebrospinal fluids pressure and cells. Urine was sent for toxicology screen and an electroencephalogram was performed.

The diagnostic tests were all within normal limits. The amount and type of medicants were rechecked with the nursing staff. While awaiting the laboratory results a second dose of 1 mg of physostigmine was given. This was given approximately 10 minutes after the initial dose of physostigmine. The effect was dramatic. The patient awoke and became alert and oriented. Deep tendon reflexes and Babinski response returned to normal. Neck rigidity was no longer obtainable. Surgery was cancelled, and the patient was sent back to her room. The following day she had an exploratory laparotomy which was entirely uneventful. No premedication was given; the anesthetic agents used included morphine sulfate and halothane. The patient was awake at the end of the procedure.

## Discussion

Although the symptoms of the central anticholinergic syndrome are many (Table) rigidity of the muscles of the neck in the form of meningismus has not

**TABLE**

**Symptoms of Central Anticholinergic Syndrome(1-5)**

Restlessness
Agitation
Confusion
Combativeness
"Plucking and Picking"
Uncooperativeness
Hysterical behavior
Memory disturbance
Visual aberration
Visual hallucinations
Auditory hallucinations
Delirium
Dysarthria
Vertigo
Hyperreflexia
Opisthotonos
Convulsions
Stupor
Coma
Babinski sign(5)

---

* Assistant Professor.

† Resident.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305. Accepted for publication September 17, 1979.

Reprint requests to Dr. Samuels.

been described. Muscle rigidity is known to occur with phenothiazine drugs as an extrapyramidal reaction. This was not considered in our patient because no phenothiazine drugs had been administered. Muscle rigidity may also occur when opiate drugs are administered rapidly.[2] Pronounced degrees of muscle rigidity are noted with nitrous oxide and opiates but are reversed immediately upon administration of an antagonist to the narcotic.[3] The increased muscle tone that appears after the administration of opiate drugs may interfere with the muscles of respiration but has not been reported to affect the paravertebral muscles. In our patient the synergism of hydroxyzine hydrochloride and meperidine combined with decreased liver function and low serum albumin levels may have contributed to the profound central nervous system depression. In addition, cancer patients who are habitually receiving opiate drugs for pain control will actually maintain a steady or even decreasing analgesic requirement.[4]

Therefore, the meperidine may have added to the comatose state but probably had no effect on muscle rigidity. This is verified by the persistance of meningismus following the administration of 0.8 mg of naloxone. It is reasonable to suppose that the cause of the meningismus was scopolamine. Signs of an anticholinergic syndrome were present. The central anticholinergic syndrome was readily reversed by physostigmine.[6] The meningismus, along with other signs mentioned, was also reversed abruptly after the physostigmine, but not after naloxone.

In summary, we report a case of neck muscle rigidity or meningismus that has not previously been described as a sign of the central anticholinergic syndrome. Meningismus accompanying other signs of a central anticholinergic syndrome including deep tendon reflexes, positive Babinski sign, and coma can be mistaken for a cerebrovascular accident. Once recognized, the syndrome can be readily reversed by physostigmine.

## REFERENCES

1. Longo VG: Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacol Rev 18:965–996, 1966
2. Gergis SD, Hoyt JL, Sokol MD: Effects of Innovar and Innovar plus nitrous oxide on muscle tone and H reflex. Anesth Analg 50:743–747, 1971
3. Hamilton WK, Cullin SC: Effect of levallorphan tartrate upon opiate induced respiratory depression. Anesthesiology 14:530–554, 1953
4. Twycross RG, Wald SL: Long-term use of diamorphine in advanced cancer, in Advances in Pain Research and Therapy. Edited by JJ Bonica and D Albe-Fessared. New York, Raven Press, 1976, Vol 1, pp 653–661
5. Forrer GR, Miller JJ: Atropine coma: a somatic therapy in psychiatry. Am J Psychiatry 115:455–458, 1958
6. Duvoisin RL, Katz R: Reversal of central anticholinergic syndrome in man by physostigmine. JAMA 206:1963–1965, 1968

# letters TO THE EDITOR

## Congenital Complete Heart Block

To the Editor:

In their article anesthetic management of congenital complete heart block (CCHB) (Anesth Analg 58:334-336, 1979) Drs Diaz and Friesen conclude ... "prophylactic preoperative insertion of a transvenous pacemaker ... is probably not necessary in most children with CCHB ... The majority of these children can be managed with adequate vagolysis and avoidance of drugs having negative chronotropic effects." They recommend that prophylactic preoperative pacing should be limited to those children with special indications for this (i.e., those with a history of Adams-Stokes attacks, no chronotropic response to atropine, QRS interval more than 0.10 seconds, exercise intolerance, history of congestive cardiac failure, or other cardiac lesion).

At The Hospital for Sick Children in Toronto we prefer to insert routinely a transvenous pacemaker preoperatively in all children with CCHB who require general anesthesia. We feel that the risk related to transvenous pacemaker insertion likely is negligible when compared to the undetermined risk of serious arrhythmia during the operation or in the perioperative period. To establish the means to pace by transthoracic or transvenous methods should this be required once surgery has commenced may involve considerable delay.

Drs Diaz and Friesen have reported on one patient with uncomplicated CCHB who was successfully managed during general anesthesia without insertion of a pacemaker. We are not convinced that this is sufficient evidence on which to base their recommendation. Children with uncomplicated CCHB only very rarely present for anesthesia, and there are no reports in the literature of additional experience with general anesthesia. In addition, it is recognized that quite apart from the interventions of anesthesia and surgery some children with apparently uncomplicated CCHB may develop serious arrhythmias and syncope requiring pacemaker therapy. It would seem to us that there is an increased potential for such arrhythmias to occur during and after general anesthesia however carefully this is conducted, and that preoperative transvenous pacemaker insertion as a routine is the safest course of action.

D. J. Steward, MB, FRCP (C)
*Anaesthetist-in-Chief*
T. Izukawa, MB, FRCP (C)
*Departments of Anaesthesia and Cardiology*
*The Hospital for Sick Children*
*555 University Ave*
*Toronto, Ontario, Canada*
*M5G 1X8*

## Obesity Supine Death Syndrome

To the Editor:

We found the article on obesity supine death syndrome by Tsueda et al (Anesth Analg 58:345-347, 1979) useful and informative. We realize that many anesthesiologists will be faced with the care of similar patients in the future. We have also found another method of handling morbidly obese patients which other anesthesiologists may find useful as reported in 1977[1] and as referred to in a previous publication reporting a series of 88 massively obese patients in 1975.[2]

Our patient had on admission a $Pa_{O_2}$ of 40 torr and a $Pa_{CO_2}$ of 65 torr. During a 2-week period, he derived no benefit from diet, physiotherapy, and respiratory therapy. Use of medroxyprogesterone, 100 mg IM, daily without interruption of the above regime, resulted, however, in reversal of blood gas values: i.e., $Pa_{O_2}$ 64 torr and $Pa_{CO_2}$ 40 torr in 2 weeks.

We believe that anesthesiologists caring for these patients should use every possible treatment to obtain an improvement in $Pa_{O_2}$ prior to subjecting them to any anesthesia technique. Along with the usual methods of increasing cardiac output and improving their ventilatory state, progesterone either by intramuscular injection or sublingually[3] is worthy of trial.

Ray McKenzie, MD
*Professor of Anesthesiology*
*University of Pittsburgh School of Medicine*
*Director of Anesthesiology*
*Magee-Womens Hospital*
*Pittsburgh, Pennsylvania 15213*
Rajindar K. Wadhwa, MD
*Assistant Professor of Clinical Anesthesiology*
*University of Pittsburgh School of Medicine*
*Staff Anesthesiologist*
*Magee-Womens Hospital*

REFERENCES

1. McKenzie R, Wadhwa RK: Progesterone for the Pickwickian syndrome: respiratory implications. Anesth Analg 56:133-135, 1977
2. McKenzie R, Figallo EM, Tantisira BT, et al: Anesthesia for jejunoileal shunt: review of 88 cases. Anesth Analg 54:65-70, 1975
3. Sutton FD Jr, Zwillich CW, Creagh CE, et al: Progesterone for outpatient treatment of Pickwickian syndrome. Ann Intern Med 83: 476-479, 1975

# book REVIEWS

## Mechanisms of Pain and Analgesic Compounds, edited by R. F. Beers and E. G. Bassett. New York, Raven Press, 1979, 510 pp., $39.50.

This book is a compilation of papers presented at a Miles Laboratories Symposium that provided a forum for communication between multidisciplinary specialists doing research and clinical work in the field of pain. The title accurately indicates that the emphasis is on the mechanisms of pain, and these discussions are conveniently grouped in sections that distinguish between those of a central and peripheral nature. Other sections include an up-to-date review of the anatomy of pain circuitry, the mechanisms of opioid analgesia and dependence, and the development of new analgesic substances.

The introductory chapters highlight the critical need for more interaction between pain specialists and quickly bring to light the significant distinctions between acute and chronic pain. These differences are raised in subsequent sections of the book to contribute to the continuity of thought and to emphasize this fundamental point. There is a logical coordination of sections and chapters in the book overall and it is well referenced.

The discussions of the molecular and neurophysiologic mechanisms of pain are well written by recognized national and international authorities actively involved in this research. The material is up-to-date, nonrepetitious, and honest in elucidating what is currently known and supported by available evidence plus what is new and important. The authors generally reveal a refreshing degree of foresight by pointing out accomplishments necessary for the future. The sections dealing with the molecular and chemical pharmacology of analgesic compounds are adequate.

The book presents important research in an organized fashion. By providing excellent reviews of the complex mechanisms of pain, it helps bridge the gap between pain research and the clinical management of patients with pain. Both researchers and clinicians will find the book suitable for reading as a means of increasing their awareness of the ever-changing progress in pain research fields. One would hope the book might stimulate further collaboration among pain specialists for the benefit of mankind.

John C. Rowlingson, MD
Assistant Professor of Anesthesiology
University of Virginia Medical Center
Charlottesville, VA

## Selected Papers in Respiratory Therapy, Second Edition, by T. J. DeKornfeld. Garden City, New York, Medical Examination Publishing Co., Inc., 1979, 542 pp., $20.00.

Second edition publications are rarely reviewed unless significantly different from the first. Dr. DeKornfeld's first edition of *Selected Papers in Inhalation Therapy* was published in 1971 and was a compilation of published articles on respiratory therapy from 1967 through 1970. The first edition was compiled during the embryonic era of organized respiratory therapy and intensive care. Thus, with the first edition, Dr. DeKornfeld assumed the risky role of being both curator and seer in the field of respiratory therapy. Many of the articles in the first edition are pertinent today while others are of historic significance putting into perspective the advances that have been made in this area over the past decade.

The second edition is an entirely different assemblage of publications on respiratory therapy from the years 1973 through 1977. This edition follows the same format as the first and is submitted as an update prompting this review. There are 52 articles grouped into nine major categories: structural and junctional considerations of the lung; pathology; intermittent positive pressure breathing; chronic obstructive pulmonary disease; complications; pediatrics; water, fire and other disasters; what's new; and miscellaneous. Each article is a reprint of the original as it appeared in the journal from which it was collected.

The section on structural and functional considerations of the lung (nine articles) is outstanding and the sections covering pediatrics and chronic obstructive lung disease are quite comprehensive. The editor included other articles of timely interest such as the moral dilemmas of the Quinlan case. The reviewer was particularly pleased to see a good review article on carbon monoxide poisoning as we are likely to see this entity more frequently resulting from our nation's altered fuel consumption habits. Too, carbon monoxide inhalation is already the nation's number one cause of death due to poisoning.

There are several criticisms of the second edition, but I have mixed emotions as to whether or not they should be considered major or minor. The book falls short as an update in respiratory therapy. The chosen articles are encumbered by excessive publication time lag common to most reference works. The second edition was published 2 years after the date of its most recent article. This, combined with the lag time in publication of the original articles, leads one to classify this book more as an excellent reference source rather than an update. For example, this potpourri contains only two articles related to continuous positive airway pressure (CPAP or PEEP) and no articles about intermittent mandatory ventilation (IMV). It is my opinion that these two subjects were major developments in respiratory therapy during the era covered by this book. The editor included an original article by Henry Heimlich on the controversial "Heimlich maneuver" for the prevention of death by choking on foreign bodies. A nice balance would have included the American Heart Association's stand on the "modified Heimlich maneuver" disputed by Dr. Heimlich.

Excluding these criticisms, there is little doubt that Dr. DeKornfeld's choice of publications for this second edition was made more difficult by the exponential increase in articles on respiratory therapy since the first edition was published. He readily admits to having edited a capricious selection of papers but apologizes for the omission of articles that others might deem more important. The reviewer sympathizes with his plight in being denied significant articles for the second edition by either cost or lack of permission for publication. The articles that he was able to use, however, were well chosen. I have the feeling that some of the articles were cleverly selected to overcome this obstacle. For example, although only two articles were cited concerning the use of CPAP or PEEP, the bibliographies to these two articles contain the references on this subject which I would consider more important.

The price of $20.00 for the second edition is double that of the first edition, reflecting the change of our economy since 1971—but I feel that the book is worth the price as an excellent reference source for anyone teaching or practicing respiratory therapy regardless of specialty. It's worth the price as a time saver alone in mediating the conflicts of opinion that arise daily in the intensive care setting.

Noel W. Larson, MD
Associate Professor
Department of Anesthesia
Director, Intensive Care Unit
University of Arkansas for
Medical Sciences
Little Rock, AK

---

## Jamieson & Kay's Textbook of Surgical Physiology, Third Edition, by I. M. Ledingham and C. MacKay. New York, Churchill Livingstone, 1978, 381 pp., $47.50.

The reader of this third edition of Jamieson & Kay's well known textbook will find significant differences from its last appearance in 1965. The rapidly expanding needs of surgery are recognized in the multiple authorship now used and while chapters on the lymphatic system and vitamin B complex have disappeared, their needs are fully met by new material on the central nervous system, immunology, shock, and the ovary. As might be expected, the approach is clinical and of necessity certain areas are stressed more and others less than some might wish, depending on individual interests. Overall, a good balance is found for those to whom the book is addressed who are declaredly younger surgeons in the training process. For them it should be a valuable resource, for it is comprehensive, yet well selected and illustrated, and written by seasoned experts in surgically related fields, in an economical and usually lucid fashion. For the anesthesiologist, it provides less depth than desirable in a number of key areas in his specialty—as for example, the physiology of respiratory and the biochemistry of neuromuscular transmission. On the other hand, it affords an excellent perspective of what is physiologically important to his surgical colleagues.

Matthew B. Divertie, MD
Professor of Medicine
Mayo Medical School
Rochester, MN

---

## Management of the Patient-Ventilator System: A Team Approach, by K. V. Martz, J. Jointer, and R. M. Shepherd. St. Louis, C. V. Mosby Co., 1979, 254 pp., $9.95.

This is a textbook concerned with the principles of managing patients requiring mechanical ventilation. Its presentation takes the form of a softcover workbook in which pages are perforated for easy removal and placement into a ringed binder, which the authors imply may aid in the management of patients at the bedside.

The strength of the text is found in its basic format which consists of chapters that correspond to the various steps involved in evaluating patients in respiratory distress and managing them while on mechanical ventilation. Comprehension of the material is facilitated by numerous charts, tables, and algorithms in addition to various learning exercises.

The text is divided into three basic parts. Part 1 consists of creating the patient-ventilator system which deals with the basic and practical considerations such as indications for establishing mechanical ventilation, selection of airways and ventilators, and the selection of initial ventilatory parameters.

Part 2 consists of aspects of managing the patient-ventilator system such as methods of maintaining satisfactory oxygenation and acid-base balance in the patient, trouble shooting a malfunctioning ventilator, use of an algorithm for positive end-expiratory pressure (PEEP), and noting the importance of providing for patient comfort and adequate physical therapy.

Part 3, which occupies approximately one half of the book, consists of exercises that can be used in the learning situation. Many of the exercises are excellent, concise vehicles for student and therapist instruction.

The weakness of the textbook is noted in its lack of indepth discussions of physiologic principles relating to patient response and ventilator function, a complete omission of references for the material presented, limitations of the types of ventilators discussed, and a minimal amount of space devoted to the use of intermittent mandatory ventilation with and without PEEP.

In general the authors have done an excellent job in presenting a significant amount of material in a concise and easily readable form. Although the clinician actively involved in critical care medicine and respiratory care would find little benefit in reading this textbook. the occasional practitioner of respiratory care, residents and medical students in training, and nurses and therapists involved in the care of patients requiring mechanical ventilation will find the book valuable. For $9.95, it's a bargain!

Eugene E. Fibuch, MD
Assistant Professor of
Anesthesiology
University of Missouri Medical
School at Kansas City
Kansas City, MO

---

## Clinical Management of the Mother and Newborn, edited by G. F. Marx. Secaucus, NJ, Springer-Verlag, 1979, 274 pp., $29.80.

*Clinical Management of the Mother and Newborn,* edited by Dr. Gertie F. Marx, a world renowned anesthesiologist in the field of obstetric anesthesia, is least of all a book on obstetric anesthesia. Rather, its appeal and usefulness encompasses all those, including obstetrician, pediatrician, anesthesiologist, and nursing personnel, dedicated to the care of the parturient and her newborn. Its impressive list of 18 contributors, seven of whom are on the faculty of the Albert Einstein College of Medicine (as is the editor), includes representatives of all phases of medicine devoted to this important area of patient care.

On inspection of the table of contents, one finds chapters on such diverse and timely topics as pathophysiology and therapy of postpartum complications, clinical neonatal neurobehavioral assessment, pulmonary function in the perinatal period, the newborn of the drug-dependent mother, and maternal and perinatal mortality; each of the chapters is written by an expert in the field. This initially gives the reader the impression that the book consists of no more than a series of unrelated topics concerning the perinatal period. Yet, despite the diversity of its contents, the unifying common bond is, as stated in the words of the editor, "This book is devoted exclusively to the first days following birth."

The topics covered in this brief work (less than 300 pages) include many new areas of interest and importance such as maternal postpartum complications, newborn evluation, the effects on the newborn of drugs taken by the mother during pregnancy and parturition, maternal-infant bonding, and complications that may be faced by the newborn including respiratory insufficiency, meconium aspiration, neonatal acidosis, and conditions warranting exchange blood transfusion. Many of the areas in which controversy exists today are covered, and while this reviewer takes issue with some of the conclusions, he feels in all instances the available data were fairly and completely covered.

Another attribute of this work is the brevity and clarity of its 15 chapters, each consisting of only 10 to 24 pages. With few exceptions, this book is a model of succinctness, yet maintains readability and good literary style without exception. Each chapter concludes with a complete bibliography of important references, emphasizing those of this decade.

This book should prove to be a welcome and useful addition to all those involved in the care of the mother and newborn.

Brett B. Gutsche, MD
Professor of Anesthesia, and
Obstetrics and Gynecology
Hospital of the University
of Pennsylvania
Philadelphia, PA

---

## Monitoring Cerebral Function, by P. F. Prior. Philadelphia, Lippincott/Harper, 1979, 366 pp., $30.00.

The title of this book is somewhat misleading, since it implies a general survey of the monitoring of cerebral function, and the book actually deals with a single instrument, the Cerebral Function Monitor (CFM). The CFM was the first, and for many years the only, commercially available EEG analysis and display device. It satisfied many of the needs for such a device: relatively low cost, simple operation, tightly compressed display, and simplicity of interpretation. However, in achieving its very simplicity, the device had to discard much of the valuable information contained in the EEG. In essence, most of the CFM's information relates to amplitude, rather than frequency. Thus, although the device does have some use for detecting major episodes of cerebral hypoxia, it does not indicate depth of anesthesia reliably. Consequently, its developers have recently expanded the usefulness of the CFM by adding information on frequency.

In this context, the book is a remarkably detailed and enthusiastic account for all the information available on the CFM. And its 366 pages and 160 illustrations reflect the fact that considerable information has been accumulated over the CFM's 10 years of use. The book describes the rationale for monitoring the EEG; the technical features of the device; some physiologic and pathologic factors involved in cerebral function; and the use of the CFM in the intensive care unit, the delivery room for fetal monitoring, and the operating room, particularly during cardiac, vascular, and neurosurgical procedures. I can recommend the book for anyone who is using or planning to use the CFM, is developing an EEG monitoring system, or is a serious student of EEG monitoring.

N. Ty Smith, MD
Professor of Anesthesia
University of California,
San Diego
San Diego, CA

## BOOK NOTES

### Applied Respiratory Physiology, Second Edition, by J. F. Nunn. Woburn, MA, Butterworths, 1979, 524 pp., $39.95.

This second edition is ample testimony to the enormous advances in knowledge of pulmonary physiology during the ensuing 8 years after the first edition. Several sections have been extremely revised, and eight new sections have been added to deal with matters little known in 1969. The author has included the International System of Units (SI) as well as conventional terminology for all values.

This volume represents a valuable and easy to use source of pulmonary physiology for the clinician.

### Anesthesiology: A Manual of Concept and Management, Second Edition, by C. W. Quimby, Jr. New York, Appleton-Century-Crofts, 1979, 384 pp., $12.50.

The second edition of this book is larger than the first edition by 32 pages. The 384 pages are nicely laid out and easy to read. The type stands out from the page in sharp contrast. Like the earlier edition, it has paper covers. It has new or expanded information on balanced anesthesia, positioning, spinal anesthesia, and postanesthetic ventilatory management. The chapter on obstetric anesthesia has been largely rewritten and now includes a section on fetal monitoring. A new "Chapter" has been included on pain and chronic discomfort but unfortunately it is only 3 pages long! More time is spent on methoxyflurane than on enflurane. It seems appropriate that a 1979 edition would more generously discuss this widely used agent. On page 151, a table of "Commonly Used Anesthetic Agents" lists cyclopropane, ether, methoxyflurane, and *ethylene*, but omits enflurane. Dr. Quimby begins his preface by giving the "aim" of his book. It is designed for people having their "first clinical experience in anesthesiology." While this is an admirable goal, it places him up against some pretty formidable competition.

## BOOK RECEIVED

**Controversy in Anesthesiology,** by J. E. Eckenhoff. Philadelphia, WB Saunders Co, 1979, 312 pp, $22.00.

# A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

## Editorial Policies

Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

**Types of materials.** The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

**Peer review.** All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

**Legal and ethical considerations.** Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

**Editing.** All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

## Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

**Title Page.** The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

**Abstract and Key Words.** The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Define all abbreviations except those approved by the International System of Units.

*Key (indexing) terms.* Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract.

**Text.** The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

*Introduction.* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods.* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

*Results.* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

*Discussion.* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**References.** (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus*. Consult the "List of Journals Indexed," printed annually in the January issue of *Index Medicus*.

Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

*Journal*

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

*Books and Other Monographs*

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

**Tables.** Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

**Illustrations.** Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of *original* drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 12.7 by 17.3 cm (5 by 7 in) but no larger than 20.3 by 25.4 cm (8 by 10 in). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them using paper clips. Do not bend figures.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with background.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, *regardless of authorship or publisher*, except for documents in the public domain.

For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Some journals publish illustrations in color only if the author pays for the extra cost.

**Legends for Illustrations.** Type legends for illustrations double spaced, starting on a separate page with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

**Abbreviations.** Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

Applicants are invited from suitably experienced Anesthesiologists to apply for the following opportunities with the faculty rank of associate professor or professor. Appointees will be permitted private practice under the aegis of the Medical Center's Professional Service Plan and will be eligible for fringe benefits according to rank. Candidates must possess diploma of American Board of Anesthesiology or its equivalent.

**DIRECTOR OBSTETRICAL ANESTHESIA:** Duties will include supervision of obstetrical anesthesia, teaching of medical students in the Depts. of Obstetrics and Anesthesiology and instruction of residents in anesthesiology. Candidate must have experience in teaching, research experience is desirable.

**ASSISTANT OR ASSOCIATE PROFESSOR ANESTHESIOLOGY:** Candidates with interest in the treatment of chronic pain. It is currently envisioned that initially 3 days per week would be allocated to clinical anesthesia and 2 days to pain therapy.

**ASSISTANT OR ASSOCIATE PROFESSOR DIVISION OF CARDIOTHORACIC SURGERY:** The division currently performs more than 350 open heart operations annually. A number which is increasing. Applicant will have the opportunity to participate in ongoing perfusion research in association with 5 full time biomedical engineers.

Submit c.v. to: David C. C. Stark, M.D., Professor and Chairman, Dept. of Anesthesiology,

THE MOUNT SINAI
MEDICAL CENTER
One Gustave L. Levy Place, New York, N.Y. 10029

*An Equal Opportunity Employer M/F*

---

***Los Angeles County University of Southern California Medical Center***

***is seeking Anesthesiologists at all levels***

to join a growing, forward-looking faculty. We are a large public medical center and primary teaching hospital of the University of Southern California and offer a diverse clinical base: one of the most challenging and sizeable in the nation. Positions offered entail clinical and teaching responsibilities with optional research opportunities in obstetrics, neuro, respiratory, and general anesthesia. Successful candidates will possess a strong desire to teach and participate in the building of an outstanding clinical and educational program in anesthesia.

*Send C. V. to* **Glenn F. Gordon, M.D.**
**Department of Anesthesiology,**

**Los Angeles County/**
**University of Southern California**
**Medical Center**
1200 North State Street
Los Angeles, CA 90033

---

CLEVELAND CLINIC
DEPARTMENT OF CARDIO-THORACIC ANESTHESIA

Positions available for "Clinical Fellow" at the Cleveland Clinic Foundation, Department of Cardio-Thoracic Anesthesia in January and July of 1980.

The positions are for anesthesiologists who have finished residency and desire advanced training in all aspects of anesthesia for open heart thoracic surgery and intensive care. Research facilities available for interested candidates. Appointments for one year or more. Attractive starting salaries commensurate with previous training. Interviews will be arranged at our expense. Please send curriculum vitae to:

Department of Cardio-Thoracic Anesthesia
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44106

For further information, call (216) 444-2595

---

*coming up next........*

**I.A.R.S. - 54th Congress**

MGM GRAND HOTEL

RENO, NEVADA

**March 9-13, 1980**

# classified ADVERTISING

**MISSOURI**

Anesthesiologist wanted to join private group practice. 400-bed hospital with all specialties except open heart; little OB. Town of 100,000 with good schools, close airport, and good recreation. Compensation package open for negotiation. Reply to Box 7-79-A, c/o I.A.R.S.

**CALIFORNIA:**

Board Eligible or Certified Anesthesiologist to join a group in Los Angeles. Must be experienced in open heart surgery. Please reply to Box 1-80-A, c/o I.A.R.S.

**PRACTICE OF ANESTHESIOLOGY—**

2-man partnership seeking 3rd. 200 bed general hospital, wide range active medical staff. Send inquiries to Box 1-80-B, c/o I.A.R.S.

**NEW YORK:**

Seeking Chief of Anesthesiology who is Board Certified with a minimum of five years clinical experience, available as early as is practicable in 1980, to head a combined Anesthesia Dept. consisting of six physician anesthesiologists serving one 126 bed general hospital and one 240 bed general hospital, in Nassau County, New York. Partnership and compensation arrangements, flexible and open for discussion. Please send complete curriculum vitae to: Professional Anesthesia Associates, 800 Front Street, Hempstead, N. Y. 11550.

**TULANE UNIVERSITY, NEW ORLEANS, LA.**

Position available in July 1980 for an academic anesthesiologist with major interest in obstetrical anesthesia, teaching and research. Tulane University is an Affirmative Action/Equal Opportunity Employer. Send Curriculum Vitae to: Robert R. Kirby, M.D., Department of Anesthesiology, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112.

**ANESTHESIOLOGIST—**

70-physician multispecialty group in Western Kentucky, expanding to 80 plus physicians and surgeons; excellent opening in section of four M.D. anesthesiologists and nine C.R.N.A.'s; new 401-bed hospital opening December 1979; early partnership with incentive income distribution formula. Subspecialty interest in cardiovascular surgery and conductive anesthesia desirable but not mandatory. Contact: Medical Director, Trover Clinic, Madisonville, Kentucky 42431: 502-821-7171, Extension 205.

**FLORIDA:**

Tampa General Hospital seeks board certified anesthesiologist to direct the Department of Anesthesiology. 600 bed hospital with all surgical specialties represented. In excess of 10,000 procedures yearly. Affiliated with the University of South Florida College of Medicine. Florida license required. Opportunity for part time private practice. Five years experience required. For further information, contact: Thomas E. McKell, M.D., Director of Professional Services, Tampa General Hospital, Davis Island, Tampa, Florida, 33606. Telephone: (813) 253-0711. An equal opportunity employer.

**PENNSYLVANIA:**

Fellowship in Ob-Gyn Anesthesia. Designed to develop anesthesiology staff for maternity hospitals. Emphasis on conduction anesthesia techniques. In-depth training, clinical and teaching experience with investigative opportunities and maintenance of general anesthesia skills in gynecology, general surgery and dental surgery. Credited by the University of Pittsburgh, an equal opportunity/affirmative action employer. Pennsylvania license required. Appointment for six months or one year. Contact: R. McKenzie, MD, FFARCS (Eng.), Director of Anesthesia, Magee-Womens Hospital, Pittsburgh, PA 15213.

**NEW HAMPSHIRE—**

Anesthesiologist (or CRNA) wanted to join staff of 28 bed full service facility. Board Cert. general & vascular surgeon operating on reg. schedule & emerg. Small town, northern New Hampshire 4-season recreation area. Good schools. Group practice on premises, resp. therapist on staff. Reply to: Personnel, Upper Connecticut Valley Hospital, Colebrook, NH 03576.

**ILLINOIS:**

Immediate openings for Board Certified/Eligible Anesthesiologists—Assistant and Associate Professors. Research Opportunities. Applications with Curriculum Vitae should be forwarded to: Dr. Donald Benson, University of Chicago, Department of Anesthesiology, 950 E. 59th Street, Chicago, Ill. 60637. AN EQUAL OPPORTUNITY EMPLOYER.

**OBSTETRIC ANESTHESIA:**

Approved one-year specialty training at high-risk obstetrical unit—3,000 deliveries per year. Ample opportunity for clinical experience, teaching, clinical and animal research using chronic maternal-fetal sheep preparation. Available July 1, 1980. Contact: John B. Craft, Jr., M.D., Director, OB Anesthesia, George Washington University Hospital, 901 23rd St. NW, Washington, D.C. 20037—(202) 676-3864. An Equal Opportunity, Affirmative Action Employer.

**ANESTHESIOLOGIST**

Needed in small Minnesota city. Challenging cases, no open heart. Malpractice insurance paid. Salary first year, then buy-in. Reply to Box 9-79-H, c/o I.A.R.S.

**TEXAS:**

Immediate openings for Anesthesiologists to join Ob/Gyn Anesthesia group. Good salary and fringes. Send curriculum vitae to Box 11-79-B, c/o I.A.R.S.

# classified ADVERTISING

## ANESTHESIOLOGIST

Board certified or eligible to join 8-man group; competitive salary plus corporation benefits; insurance, dues paid; early full group membership. University-affiliated hospital. Write to: Gary S. Freeman, M.D., Mt. Sinai Hospital, Cleveland, Ohio 44106—or call collect (216) 795-6000, ext. 444.

## CHIEF ANESTHESIOLOGISTS NEEDED

for growing modern ambulatory surgical centers. All types of procedures performed. Locations throughout Florida. Send resumes to Box 9-79-C, ℅ I.A.R.S.

## ANESTHESIOLOGIST—

Board Certified, to join hospital based, multispecialty group in Northeastern Pennsylvania. Reply with CV to D. R. Weaver, M.D., Medical Director, Guthrie Clinic, Sayre, Penna. 18840.

## FELLOWSHIP IN OBSTETRICAL ANESTHESIA—

Opportunity for extensive approved one year specialty training in high-risk obstetrical unit with approximately 7000 deliveries per year and full-time obstetrical anesthesia staff. Base clinical year, two years of clinical anesthesia and FLEX required. Salary negotiable. For information contact: Albert L. Maduska, M.D., Anesthesiology, E.H. Crump Women's Hospital, University of Tennessee Center for the Health Sciences, Memphis, Tennessee 38163.

## ANESTHESIOLOGIST:

Board certified with four years of real life clinical experience, familiar with critical care medicine, able to organize and upgrade a department's activities, current in all areas of anesthesia including cardiac, neuro and pediatrics, is seeking a private practice of anesthesia involving primarily supervision and teaching but also direct patient care and departmental function, in a growing community and a hospital with great potential. Send information to Box 11-79-A, c/o I.A.R.S.

## MAYO FOUNDATION, DEPARTMENT OF ANESTHESIOLOGY—

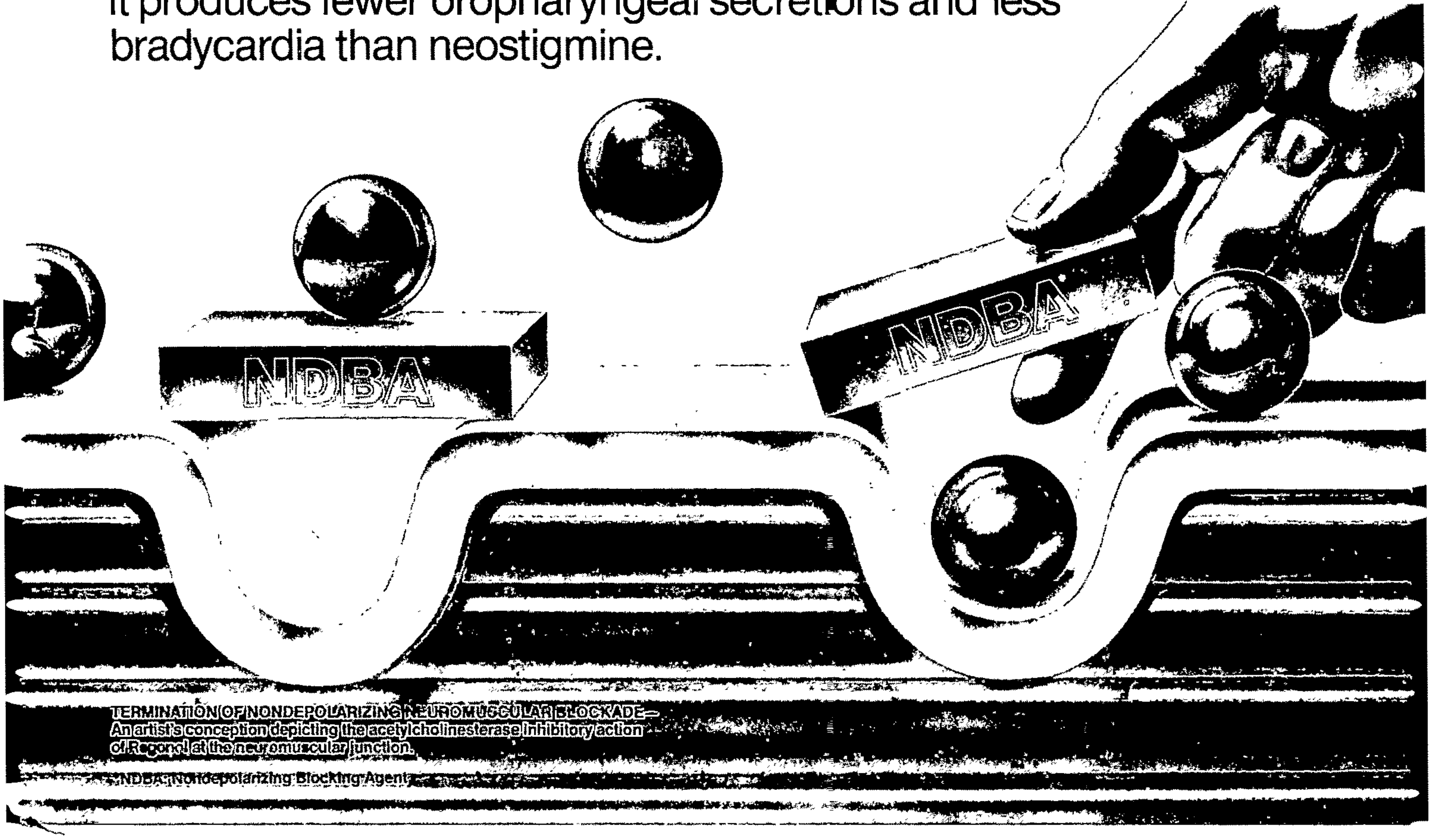
Opportunities for advanced subspecialty training in cardiovascular and neuro-anesthesia, respiratory intensive care, and pain management are available to qualified candidates. Indepth training experience in one or more of these areas for periods of six months to two years may be arranged. For additional details, contact: Alan D. Sessler, M.D., Chairman, Department of Anesthesiology, Mayo Foundation, Rochester, Minnesota 55901.

*Rates for classified advertising: $3.00 per line, minimum 5 lines; box number ads $3.50 per line. Classified display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia, 3645 Warrensville Center Rd., Cleveland, OH 44122.*

Remove the Block Yourself

# Reverse with REGONOL® pyridostigmine bromide

Regonol rapidly restores full neuromuscular transmission. It produces fewer oropharyngeal secretions and less bradycardia than neostigmine.



TERMINATION OF NONDEPOLARIZING NEUROMUSCULAR BLOCKADE—An artist's conception depicting the acetylcholinesterase inhibitory action of Regonol at the neuromuscular junction.

*NDBA: Nondepolarizing Blocking Agent

**Brief Summary** (Please consult full package insert, enclosed in every package, before using Regonol).

**INDICATIONS**—Regonol (pyridostigmine bromide) is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

**CONTRAINDICATIONS**—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

**WARNINGS**—Use with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

*Usage in Pregnancy*—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—Side effects are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—Prior or simultaneous administration of atropine sulfate (0.6 to 1.2 mg; I.V.) is recommended to minimize the side effects (excessive secretions, bradycardia). Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether.

**CAUTION**—Federal law prohibits dispensing without a prescription.

**HOW SUPPLIED**—Regonol is available in: 2 ml ampuls—5 mg/ml boxes of 10. NDC #0052-0460-10

Organon

A PART OF Akzona INC.

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# INDEX OF ADVERTISERS

Classified Advertising . . . (23), (24)
Cleveland Clinic Foundation—*Employment Opportunity* . . . (22)
Cleveland Clinic Foundation—*International Symposium* . . . (7)
J. H. Emerson Company—*IMV Ventilator* . . . (15)
KMA, Inc.—*Thermodilution Equipment* . . . (7)
Mt. Sinai Medical Center—*Employment Opportunities* . . . (22)
National Catheter Co.—*Endotracheal Tube* . . . Cover 2
Ohio Medical Products—*Ethrane®* . . . (12), (13), (14)
O'Neal, Jones & Feldman—*Antilirium* . . . (16), (17)
Organon Pharmaceuticals—*Hexadrol®* . . . (10), (11)
Organon Pharmaceuticals—*Pavulon®* . . . (4), (5), (6)
Organon Pharmaceuticals—*Regonol®* . . . (25)
Pharmaseal®—*Spinal Trays* . . . Cover 4
Portex, Inc.—*Epidural Tray* . . . Cover 3
Puritan-Bennett Corp., Foregger Medical Division—*Anesthesia Equipment* . . . (8), (9)
University of Southern California—*Employment Opportunity* . . . (22)

# When you have the best Epidural Catheter, You design the best Continuous Epidural Anesthesia Tray.

**Introducing the Portex Continuous Epidural Anesthesia Tray featuring the Exclusive Portex Nylon Catheter.**

All the necessary components for the administration of Continuous Epidural Anesthesia conveniently supplied in a Sterile / Disposable Tray.

Call or write Portex, Inc. or your local Portex, Inc. Distributor for further information and descriptive brochure.

PORTEX®

Portex, Inc. 42 Industrial Way, Wilmington, MA 01887 (617) 658-5110
In Canada: 1361 Huntingwood Drive, Scarborough, Ontario

# INTRODUCING THE NEW "C" SERIES SPINAL TRAYS.

# THEY MAKE A POINT FOR SAFETY.

**There's a very important safety point in our new "C" Series spinal tray line: An exclusive 5 micron filter aspiration needle.**

This 19 ga. x 1½" needle contains a 5 micron particulate matter filter in its hub, which provides assurance against the inadvertent injection of glass ampule particles into the subarachnoid space.

It comes preattached to our clear 5 cc syringe, another safety feature which allows complete visualization of the drug mixture.

## PLUS, ALL THESE OTHER SAFETY AND CONVENIENCE POINTS, TOO.

**A light, clean spinal needle.** We use our own spinal needle with a metal hub and lightweight nylon tip stylet which is much less likely to dislodge.

And both cannula and stylet are match ground to guard against accidental tissue coring.

**Brand name drugs you can rely on,** with a variety of spinal anesthetics including Pontocaine,* Xylocaine** and Lyophilized Pontocaine; plus a choice of vasoconstrictors.

There's also a clean styrene basin with no styrofoam particles to flake off on your gloves; a sterilization indicator; three unique prep swabs and much more.

And the price is definitely a point in your favor.

Be sure to see our new "C" series.

For samples, just contact your Pharmaseal representative.

PHARMASEAL®
GLENDALE, CA 91201

*Pontocaine is Winthrop Laboratories' trademark
**Xylocaine is Astra Pharmaceutical Products' trademark

Rec.
11.6.80

ISSN 0003-2999
vol. 59, no. 2 February 1980

# Anesthesia and Analgesia

Journal of the International
Anesthesia Research Society

OLDEST PUBLICATION IN THE SPECIALTY –
ESTABLISHED 1922

COLLEGE OF MEDICINE · U. I. · UNIVERSITY
LIBRARY

**LaBarge Mon-a-therm**®

# Surgical Temperature Monitoring System

DISPOSABLE SENSORS:

- rectal
- tympanic
- esophageal
- esophageal stethoscope temperature sensor (EST) sizes 12, 18, 24 French

Mon-a-therm™
3. SWITCH AT TEMP — READ PATIENT TEMPERATURE
1. SWITCH AT 86 SET TO 86°
2. SWITCH AT 108 SET TO 108°
86
108
OFF
TEMP
WHITE DOT AT TOP REPLACE BATTERIES
LaBarge inc
503-0021
503-0099
24 French
503-0048
12 French
503-0056
18 French
LaBarge Mon-a-therm esophageal/rectal temperature sensor
LaBarge Mon-a-therm esophageal stethoscope temperature sensor

- new improved cable connector assembly with RFI filter is easy to use, and provides reliable electrical contact with disposable sensor.

**Now provides a unique family of disposable temperature sensors…**
**…to let you continuously monitor temperature trends at the site you prefer.**
**Accurately. Economically.**

The Mon-a-therm System can provide a vital indication of problematic temperature trends that may confront any anesthetized patient.

Find out more about our family of disposably-priced temperature sensors, our improved cable connector, and the entire Mon-a-therm System.

**LaBarge inc**

Medical Products Division
500 Broadway Building
St. Louis, MO 63102

Call LaBarge today:
Toll Free 800 325-3363
In Missouri 314 231-3400

# Anesthesia and Analgesia

Journal of the
International Anesthesia Research Society

3645 Warrensville Center Road
Cleveland, Ohio 44122
Telephones (216) 295-1124, 295-1130

## EDITORIAL BOARD

**Editor in Chief:**
**Nicholas M. Greene, M.D.,** New Haven, Connecticut

**Editors:**
**D. Ryan Cook, M.D.,** Pittsburgh, Pennsylvania
**Douglas B. Craig, M.D.,** Winnipeg, Manitoba
**E. Paul Didier, M.D.,** Rochester, Minnesota
**Ronald W. Dunbar, M.D.,** Atlanta, Georgia
**Alison B. Froese, M.D.,** Toronto, Ontario
**John P. Kampine, M.D.,** Milwaukee, Wisconsin
**David E. Longnecker, M.D.,** Charlottesville, Virginia
**John J. Savarese, M.D.,** Boston, Massachusetts
**N. Ty Smith, M.D.,** San Diego, California
**Robert K. Stoelting, M.D.,** Indianapolis, Indiana

**Book Review Editor:**
**E. Paul Didier, M.D.,** Rochester, Minnesota

**ANESTHESIA AND ANALGESIA** (ISSN 0003-2999) is published monthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, M.D., Bruce F. Cullen, M.D., E. Paul Didier, M.D., Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., B. B. Sankey, M.D., and Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris T. Nicholson, M.D., and T. H. Seldon, M.D.

**EDITORIAL CORRESPONDENCE** and manuscripts should be addressed to: **Nicholas M. Greene, M.D., Editor in Chief, Anesthesia and Analgesia, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: [203] 436-2887).** For information concerning preparation of manuscripts see "A Guide for Authors" published in each issue. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

**BOOKS FOR REVIEW** should be sent directly to the Book Review Editor, **E. Paul Didier, M.D., ℅ Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55901.**

**REPRINTS:** For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

**BUSINESS CORRESPONDENCE,** including subscription and membership payments, single issue purchases, change of address notices, and requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122 (Telephones: [216] 295-1124, 295-1130).**

**SUBSCRIPTION RATES:** United States and U.S. possessions, $30.00 per year (12 issues); all other countries, $33.00.

**MEMBERSHIP DUES (Including Journal Subscription):** United States and U.S. possessions, $30.00 per year; all other countries, $33.00. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). **Educational Membership** (half the full price) available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only, upon completion of application including certification by applicant's program director.

**SINGLE ISSUES:** $5.50 each beginning 1979; $4.50 for years 1970–1978; $3.00 for years 1954–1969; $2.00 for years 1928–1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

**MAILING DATES:** Journals mailed 25th of month preceding issue date. Second class postage paid at Cleveland, Ohio and at additional mailing offices.

**CHANGE OF ADDRESS NOTICES:** Send to Cleveland business office as much in advance as possible to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable. POSTMASTER: Send address changes to Anesthesia and Analgesia, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

**ADVERTISING:** Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086 (Telephone: [609] 848-1000). Orders, contracts, and classified ad copy should be sent to the Cleveland office. Reproduction materials and inserts should be sent to Waverly Press, Inc., 300 Idlewild Avenue, Easton, Maryland 21601.

© 1980, International Anesthesia Research Society

# Anesthesia and Analgesia

## EDITORIAL

The World Federation of Societies of Anesthesiologists and You—Gomez QJ ..... 87

## SCIENTIFIC ARTICLES

Obesity and the Cephalad Spread of Analgesia following Epidural Administration of Bupivacaine for Cesarean Section—Hodgkinson R, and Husain FJ ....... 89

Cardiovascular Responses to Nitrous Oxide Exposure for Two Hours in Man—Kawamura R, Stanley TH, English JB, Hill GE, Liu W-S, and Webster LR ... 93

A Weak Negative Inotropic Effect of Protamine Sulfate upon the Isolated Canine Heart Muscle—Iwatsuki N, Matsukawa S, and Iwatsuki K ............... 100

Analysis of Ventilatory Depression by Enflurane during Clinical Anesthesia—Wahba WM ............... 103

Clinical Characteristics of Long-Term Succinylcholine Neuromuscular Blockade during Balanced Anesthesia—Ramsey FM, Lebowitz PW, Savarese JJ, and Ali HH ............... 110

Nitroglycerin and the Neuromuscular Blockade Produced by Gallamine, Succinylcholine, *d*-Tubocurarine, and Pancuronium—Glisson SN, Sanchez MM, El-Etr AA, and Lim RA ............... 117

Airway Responses in Normal Subjects following Topical Anesthesia with Ultrasonic Aerosols of 4% Lidocaine—Gal TJ ............... 123

Comparison of Cardiovascular Responses to Anesthesia and Operation When Intravenous Lidocaine or Morphine Sulfate Is Used as Adjunct to Diazapam-Nitrous Oxide Anesthesia for Cardiac Surgery—Knight PR, Kroll DA, Nahrwold ML, Denlinger JK, Kirsh M, Welter LO, Hill AG, Cohen PJ, and Ronfeld RA ............... 130

## SPECIAL ARTICLE

The History of Drug Inhalation: A Brief Overview—Gravenstein JS ............. 140

## CLINICAL REPORTS

Hepatitis Associated with Enflurane Anesthesia—Ona FV, Patanella H, and Ayub A ............... 146

A Serious Anesthetic Hazard during Orthognathic Surgery—Fagraeus L, Angelillo JC, and Dolan EA ............... 150

# Contents

February 1980
Volume 59/Number 2

---

**Dangerous Rise in Pulmonary Wedge Pressure following Aortography in a Patient with a Pheochromocytoma**—Rouby JJ, Gory G, Gaveau T, Glaser P, and Viars P . . . . 154
**Pruritis following Spinal Anesthesia**—Koski DW, and Fraser JG . . . . 157
**Hydromediastinum after Placement of a Thermodilution Pulmonary Arterial Catheter**—Gordon EP, Quan SF, and Schlobohm RM . . . . 159

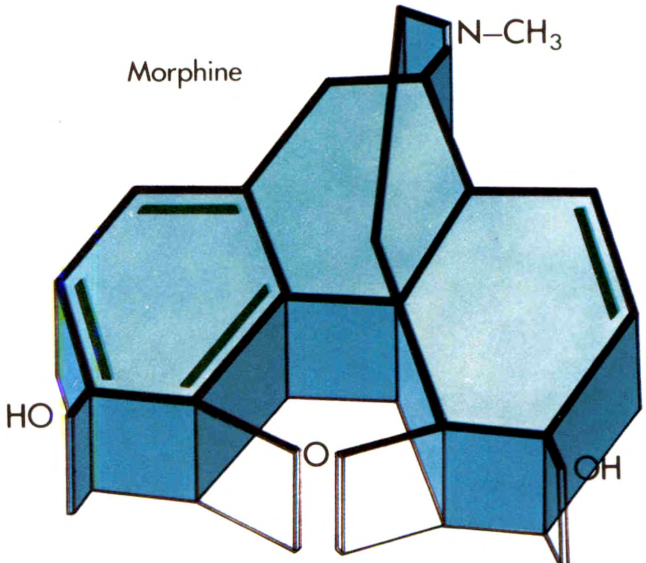
## LETTERS TO THE EDITOR

**Microwave Rewarming**—Lees DE, and Schuette W; reply by Westenskow DR, and Wong KC . . . . 161
**Hazards of Scavenging Systems**—Milliken RA . . . . 162
**Bradycardia after Intravenous Fentanyl during Subarachnoid Anesthesia**—Hilgenberg JC, and Johantgen WC . . . . 162
**Scavenging of Anesthetic Gases**—Aldrete JA, and Virtue RW . . . . 163

## BOOK REVIEWS

**Principles and Practice of Blood-Gas Analysis**—Adams AP, and Hahn CEW . . . . 165
**Advances in Pain Research and Therapy**—Bonica JJ, Liebeskind JC, and Albe-Fessard DG . . . . 165
**The Recovery Room**—Drain CB, and Shipley SB . . . . 165
**Pediatric Respiratory Therapy, Second Edition**—Lough MD, Doershuk CF, and Stern RC . . . . 166
**Manual of Pediatric Anesthesia**—Steward DJ . . . . 167
**Seminars in Respiratory Medicine**—Petty TL, and Cherniack RM . . . . 167

# Now...in moderate to severe pai



**Important option when potent parenteral analgesics are indicated**

- Standard doses of Stadol are as effective in relieving pain as standard doses of both morphine[1-4] and meperidine.[5-7, 37]

- By either I.M. or I.V. route—provides prompt onset of analgesia, achieves peak activity rapidly, maintains effects for 3–4 hours.

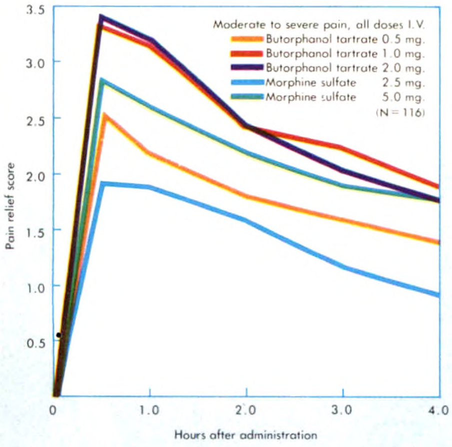
- Distinguished by its favorable side effects profile,[1-16, 31-33, 36, 37]—low physical-dependence liability, limited respiratory depressant effect, little nausea and vomiting, and low incidence of CNS effects other than sedation.

- 2 mg. of Stadol produces an order of respiratory depression similar to that caused by 10 mg. of morphine. In contrast to morphine, increasing Stadol doses yield greater analgesic effect,[9] without appreciably increasing liability for respiratory depression.[16]

- The low addictive potential of Stadol[24] is underscored by its narcotic antagonist properties.

**Stadol is not recommended for patients physically dependent on narcotics or with significant previous narcotic experience. Its use in such patients, without prior detoxification, will result in induction of withdrawal reactions.**

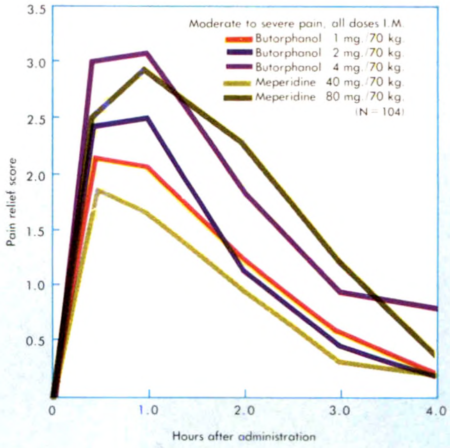
## Unsurpassed pain relief



**Average mean pain relief scores**
In response to butorphanol tartrate and morphine sulfate

**In this study "...butorphanol tartrate 0.5 mg produced greater relief than morphine sulfate 2.5 mg and butorphanol tartrate 1.0 and 2.0 mg produced greater relief than morphine sulfate 5.0 mg."** **(DelPizzo[1])**

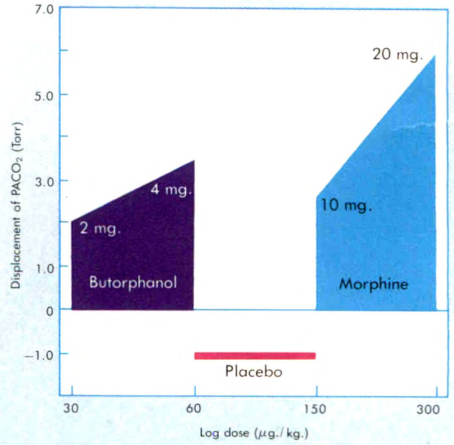
## Unsurpassed pain relief



**Average mean pain relief scores**
In response to butorphanol tartrate and meperidine hydrochloride

**In moderate to severe pain, butorphanol tartrate provided relief "...that was not statistically distinguishable from that achieved with 80 mg/70 kg meperidine."** **(Gilbert et al[5])**

## Limited respiratory depressant effect

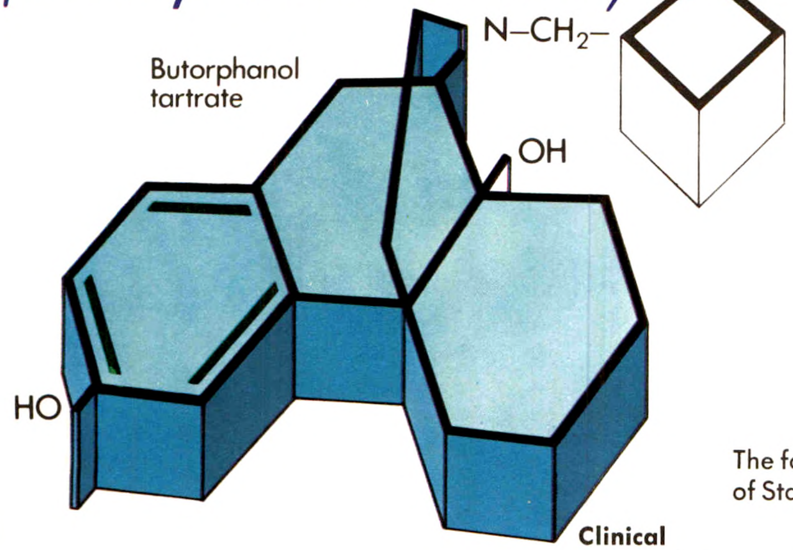


Log dose PACO2 displacement curves

**In this graph based on alveolar carbon dioxide tension ($PACO_2$) measurements, the flatter the curve, the less respiratory depression. "The flat dose-response curve ...of butorphanol may indicate that, because of its antagonistic properties, there is a limit to its respiratory depressant effects.** **(Adapted from Nagashima et al[16])** **Unlike morphine with its steep dose-response curve, the magnitude of respiratory depression does not increase in a dose-related manner with Stadol within**

# Stadol® IM IV

## (butorphanol tartrate)



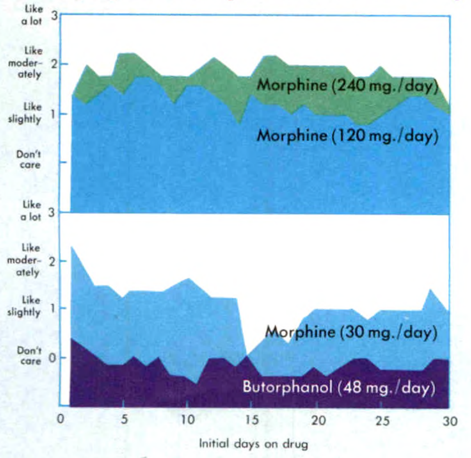
# closer to the ideal parenteral analgesic

The following table shows a side-by-side clinical comparison of Stadol with both morphine and meperidine.

| Clinical parameters | Meperidine | Morphine | Stadol |
|---|---|---|---|
| Control status | Schedule II | Schedule II | Nonscheduled |
| Indication | moderate to severe pain | moderate to severe pain | moderate to severe pain |
| Standard I.M. dose | 75–100 mg. | 8–10 mg. | 2 mg. (1 to 4 mg.) |
| Standard I.V. dose | 50–100 mg. | 4–10 mg. | 1 mg. (0.5 to 2 mg.) |
| Usual route of administration | I.M./I.V. | I.M./I.V. | I.M./I.V. |
| Onset of pain relief | 30 minutes I.M., very rapidly I.V. | 30 minutes I.M., very rapidly I.V. | less than 30 minutes I.M., very rapidly I.V. |
| Peak analgesic activity | within 1 hour I.M., within 30 minutes I.V. | within 1 hour I.M., within 20 minutes I.V. | within 1 hour I.M., within 30 minutes I.V. |
| Duration of pain relief I.M./I.V. | slightly less than morphine | about 4 hours | 3–4 hours |
| Addicting potential | high | high | low |
| Respiratory effects | dose-related depression | dose-related depression | limited depression—no appreciable dose-related increase within the range of recommended doses. |

Data for this table were obtained from: Jaffe, J. H. and Martin, W. R.: Narcotic analgesics and antagonists, in The Pharmacological Basis of Therapeutics (Goodman, L. S. and Gilman, A., eds.), ed. 5, New York, Macmillan, 1975, pp. 245–283; AMA Drug Evaluations, ed. 3, Chicago, 1977, pp. 325–339; and from manufacturer recommendations.

### Low physical-dependence liability



**Preference scores completed by subjects during chronic butorphanol tartrate administration compared with scores from three other groups of subjects receiving 30, 120 and 240 mg. of morphine daily.** (Adapted from Jasinski et al[24])

**BRISTOL™** BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

In moderate.
to severe pain...

# Stadol® IM IV
## (butorphanol tartrate)

**INDICATIONS AND USAGE**— (1) 8/18/78
Stadol is recommended for the relief of moderate to severe pain.
**CONTRAINDICATIONS**—Stadol should not be administered to patients who have been shown to be hypersensitive to it.
**WARNINGS—Patients physically dependent on narcotics:** Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.
**Drug dependence:** Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical-dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.
**Head injury and increased intracranial pressure:** Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.
**Cardiovascular effects:** Because Stadol increases the work of the heart, especially the pulmonary circuit (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.
**PRECAUTIONS—Certain respiratory conditions:** Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.
**Impaired renal or hepatic function:** Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.
**Biliary surgery:** Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.
**Usage in pregnancy:** The safety of Stadol for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.
**Usage in labor and delivery:** Safety to the mother and fetus following administration of Stadol during labor and delivery has not been established.
**Usage in nursing mothers:** The use of Stadol is not recommended in nursing mothers since it is not known whether this drug is excreted in human milk.
**Pediatric use:** Safety and efficacy in children below age 18 years have not been established.
**ADVERSE REACTIONS**—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:
**CNS effects:** nervousness, unusual dreams, agitation, euphoria, hallucinations
**Autonomic effects:** flushing and warmth, dry mouth, sensitivity to cold
**Cardiovascular:** palpitation, increase or decrease of blood pressure
**Gastrointestinal:** vomiting
**Respiratory:** slowing of respiration, shallow breathing
**Dermatological:** rash or hives
**Eye:** diplopia or blurred vision
**OVERDOSAGE—Manifestations:** Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.
**Treatment:** The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors, and assisted or controlled respiration.
**DOSAGE AND ADMINISTRATION—*Adults:* Intramuscular**—The usual recommended single dose is 2 mg. This may be repeated every three to four hours, as necessary. The effective dosage range, depending on the severity of pain, is 1 to 4 mg. repeated every three to four hours. At this time, there is insufficient clinical data to recommend single doses beyond 4 mg.
**Intravenous**—The usual recommended single dose for intravenous administration is 1 mg. repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg. repeated every three to four hours.
***Children:*** Since there is no clinical experience in children under 18 years, Stadol is not recommended in this age group.
**Storage conditions:** When stored at room temperature, the stability of the solution in vials is 2 years.
**SUPPLY**—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, 2 mg. per ml., 2-ml. vial; 1 mg. per ml., 1-ml. vial; 2 mg. per ml., 1-ml. vial; 2 mg. per ml., 10-ml. multi-dose vial.
**NDC** 0015-5644–2 mg. per ml., 2-ml. vials
**NDC** 0015-5645–1 mg. per ml., 1-ml. vials
**NDC** 0015-5646–2 mg. per ml., 1-ml. vials
**NDC** 0015-5648–2 mg. per ml., 10-ml. multi-dose vials

For information on package sizes available, refer to the current price schedule.

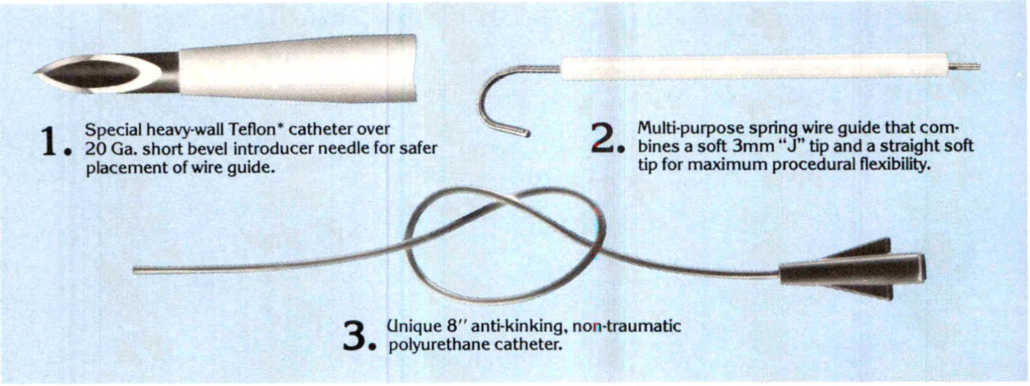
BRISTOL™
BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

MC4021 . 3/79 Printed in U.S.A.

**BUTORPHANOL BIBLIOGRAPHY:** 1. **DelPizzo, A.:** Butorphanol, a new intravenous analgesic: Double-blind comparison with morphine sulfate in postoperative patients with moderate or severe pain, Curr. Ther. Res. 20:221, 1976. 2. **Tavakoli, M. et al:** Butorphanol and morphine: A double-blind comparison of their parenteral analgesic activity, Anesth. Analg. 55:394, 1976. 3. **Dobkin, A. B. et al:** Butorphanol: A double-blind evaluation in postoperative patients with moderate or severe pain, Can. Anaesth. Soc. J. 21:600, 1974. 4. **Lippmann, M. et al:** Butorphanol and morphine: A double-blind multiple intramuscular dose comparative safety and efficacy study in patients with postoperative pain, Curr. Ther. Res. 21:427, 1977. 5. **Gilbert, M. S. et al:** Intramuscular butorphanol and meperidine in postoperative pain, Clin. Pharmacol. Ther. 20:359, 1976. 6. **Galloway, F. M. et al:** Comparison of analgesia by intravenous butorphanol and meperidine in patients with post-operative pain, Can. Anaesth. Soc. J. 24:90, 1977. 7. **Comunale, F. L. and Filtzer, H. S.:** Double-blind comparison of butorphanol, a new parenteral analgesic, and meperidine in the treatment of postoperative pain, Curr. Ther. Res. 22:116, 1977. 8. **DelPizzo, A.:** Double-blind evaluation of butorphanol and meperidine given intramuscularly before anesthesia, Curr. Ther. Res. 20:763, 1976. 9. **Dobkin, A. B. et al:** Butorphanol and pentazocine in patients with severe postoperative pain, Clin. Pharmacol. Ther. 18:547, 1975. 10. **Gilbert, M. S. et al:** Butorphanol: A double-blind comparison with pentazocine in post-operative patients with moderate to severe pain, J. Int. Med. Res. 4:255, 1976. 11. **Dobkin, A. B. et al:** Butorphanol tartrate: 1. Safety and efficacy in multidose control of postoperative pain, Can. Anaesth. Soc. J. 23:596, 1976. 12. **Bauer, R. O. et al:** Analgesic evaluation of butorphanol in patients with postoperative wound pain, Proc. West. Pharmacol. Soc. 19:266, 1976. 13. **North, W. C. and Tielens, D. R.:** A comparison of butorphanol and pentazocine as postoperative analgesics, abstracted, Clin. Pharmacol. Ther. 21:112, 1977. 14. **Kliman, A. et al:** Clinical experience with intramuscular butorphanol for the treatment of a variety of chronic pain syndromes, Curr. Ther. Res. 22:105, 1977. 15. **Zeedick, J. F.:** Butorphanol–A new, potent, parenteral analgesic, Curr. Ther. Res. 21:802, 1977. 16. **Nagashima, H. et al:** Respiratory and circulatory effects of intravenous butorphanol and morphine, Clin. Pharmacol. Ther. 19:738, 1976. 17. **Gordon, M. et al:** Approaches to the problem of opiate abuse, presented to the Committee on Problems of Drug Dependence, Proceedings, 498–513, 1974. 18. **Miller, M.:** Inhibition of ADH release in the rat by narcotic antagonists, Neuroendocrinology 19:241, 1975. 19. **Monković, I. et al:** Oxilorphan and butorphanol. Potent narcotic antagonists and nonaddicting analgesics in the 3,14-dihydroxymorphinan series, Part V, Can. J. Chem. 53:3094, 1975. 20. **Foldes, F. F. et al:** Double-blind comparison of the respiratory and circulatory effects of intravenous butorphanol and morphine, presented to the Committee on Problems of Drug Dependence, Proceedings, 373–390, 1975. 21. **Pircio, A. W. et al:** The pharmacology of butorphanol, a 3,14-dihydroxymorphinan narcotic antagonist analgesic, Arch. Int. Pharmacodyn. Ther. 220:231, 1976. 22. **Cavanagh, R. L. et al:** Antitussive properties of butorphanol, Arch. Int. Pharmacodyn. Ther. 220:258, 1976. 23. **Schurig, J. E. et al:** The effects of butorphanol and morphine on pulmonary mechanics, arterial blood pressure and venous plasma histamine levels in anesthetized dogs, Federation Meetings, Proceedings, 546, vol. 35, No. 3, 1976. 24. **Jasinski, D. R. et al:** Progress Report on Studies from the Clinical Pharmacology Section of the Addiction Research Center, Problems of Drug Dependence, Proceedings, 112–120, 1976. 25. **Dobkin, A. B. et al:** Butorphanol tartrate: 2. Safety and efficacy in balanced anesthesia, Can. Anaesth. Soc. J. 23:601, 1976. 26. **Swain, H. H. et al:** Evaluation of new compounds for morphine-like physical dependence in the rhesus monkey, Report of the Committee on Problems of Drug Dependence, addendum, 693–696, 1973. 27. **Jasinski, D. R. et al:** Progress Report on Studies from the Clinical Pharmacology Section of the Addiction Research Center, Committee on Problems of Drug Dependence, Proceedings, 136–149, 1975. 28. **Houde, R. W. et al:** Annual Report of the Analgesic Studies Section of the Memorial Sloan-Kettering Cancer Center, Reported to the Committee on Problems of Drug Dependence, Proceedings, 149–168, 1976. 29. **Kallos, T. and Caruso, F. S.:** Respiratory effects of butorphanol, abstracted, Clin. Pharmacol. Ther. 21:107, 1977. 30. **Oh, S. J.:** Experimental pentazocine-induced fibrous myopathy, Ala. J. Med. Sci. 14:64, 1977. 31. **Lippmann, M. et al:** Analgesic onset time of I.V. butorphanol in postsurgical patients: A placebo-controlled study, Curr. Ther. Res. 22:276, 1977. 32. **Andrews, I. C.:** Butorphanol and pentazocine: A double-blind intramuscular comparison in patients with moderate to severe postoperative pain, Curr. Ther. Res. 22:697, 1977. 33. **Zeedick, J. F.:** Efficacy and safety evaluation of butorphanol in postoperative pain, Curr. Ther. Res. 22:707, 1977. 34. **Roebel, L. E. et al:** The effects of butorphanol and morphine on terminal bile duct and duodenal activity in anesthetized dogs, The Pharmacologist 19:146, (Fall) 1977. 35. **Popio, K. A. et al:** Hemodynamic and respiratory effects of morphine and butorphanol, Clin. Pharmacol. Ther. 23:281, 1978. 36. **Carter, R. et al:** A double-blind clinical evaluation of butorphanol and pentazocine in the alleviation of pain following gynecological therapy, Curr. Ther. Res. 23:48, 1978. 37. **Stehling, L. C. and Zauder, H. L.:** Double-blind comparison of butorphanol and meperidine in the treatment of post-surgical pain, J. Int. Med. Res. 6:306, 1978. 38. **Monković, I. et al:** Total synthesis and pharmacological activities of N-substituted 3,14-dihydroxymorphinans, J. Am. Chem. Soc. 95:7910, 1973. 39. **Monković, I. et al:** A stereoselective total synthesis of 14-hydroxymorphinans. Grewe approach, J. Am. Chem. Soc. (accepted).

Copyright © 1979 by Bristol Laboratories

# We'll take you on a safer journey than you've ever made through the body's central veins.



1. Special heavy-wall Teflon* catheter over 20 Ga. short bevel introducer needle for safer placement of wire guide.

2. Multi-purpose spring wire guide that combines a soft 3mm "J" tip and a straight soft tip for maximum procedural flexibility.

3. Unique 8″ anti-kinking, non-traumatic polyurethane catheter.

*Du Pont Trademark

## With the only complete CVP kit. Adaptable to TPN procedures as well.

Arrow's aim is to increase safety every inch of the way. And in line with that aim, we've modified many of the components used in existing procedures. And combined them all in a series of precision-packed kits.

The Central Vein Catheterization Kit is one of them.

It aggregates all components necessary for percutaneous catheterization of any central vein (using the Seldinger technique) in one sterile package.

While specific products are available for specific sites, this product allows the physician to dictate the puncture site rather than being limited by narrow product design.

This kit is another step towards Arrow's target of maximizing safety for you and your patients.

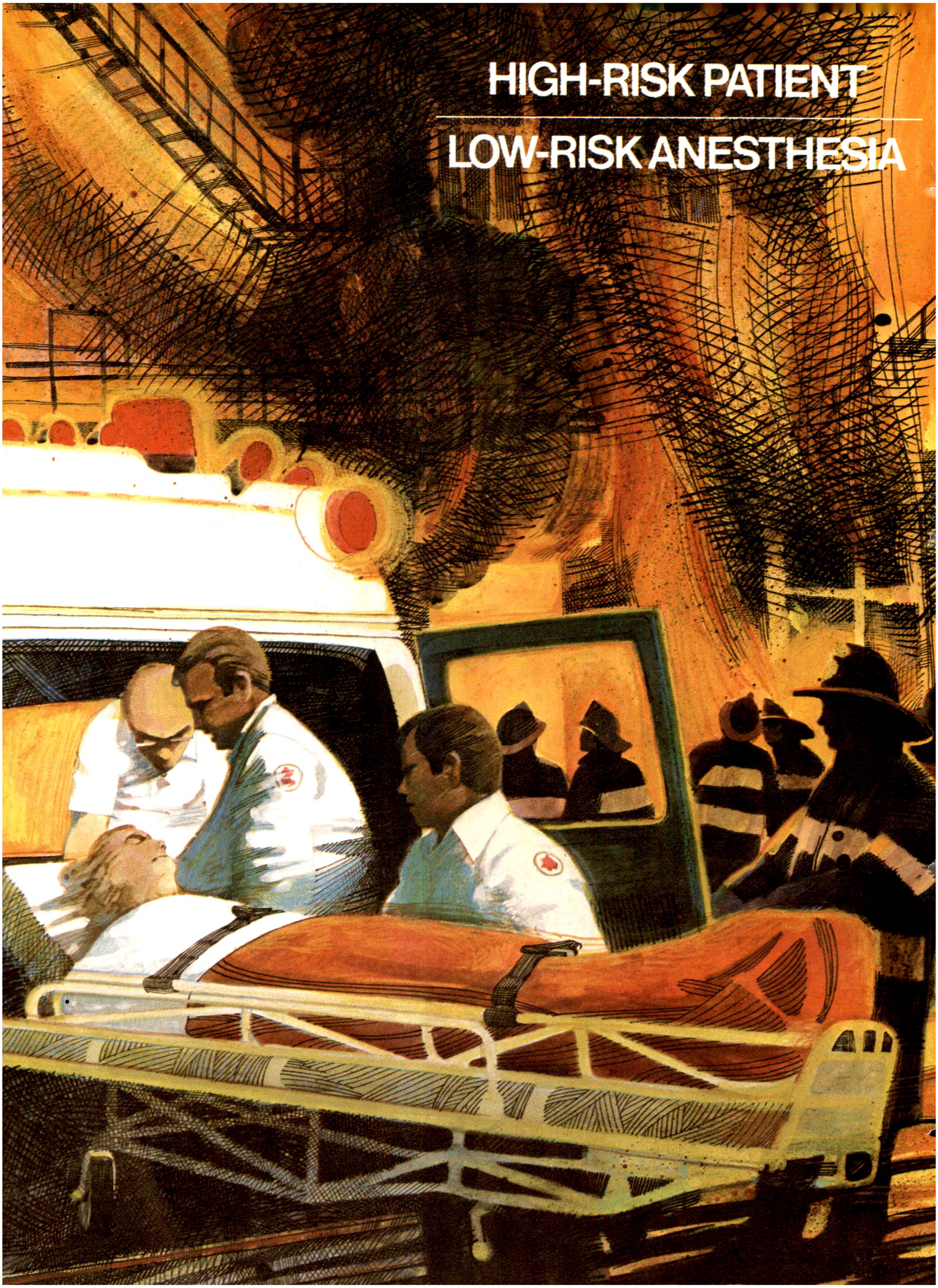
## The Arrow Central Vein Catheterization Kit

(for subclavian, external and internal jugular vein catheterization).
Product No. AK-04200

© 1979 Arrow International

**ARROW**
INTERNATIONAL, INC.

Hill and George Avenues
Reading, Pennsylvania 19610
215-378-0131 • 800-523-8446


HIGH-RISK PATIENT
LOW-RISK ANESTHESIA

# Ketalar®
## (ketamine hydrochloride injection, NF)

## Features you need...

Smooth, rapid onset of anesthesia, profound analgesia, IM or IV administration. Little risk of liver damage or buildup of tolerance following repeated procedures. Ketalar usually strengthens, rather than depresses, blood pressure, pulse rate and respiration. When necessary, it permits maintenance of unaided respiration because of minimal relaxation of skeletal muscles or laryngeal-pharyngeal reflexes.

## for the patients who need them

At either end of the age spectrum, the pediatric or geriatric patient. The patient in shock, or with shock potential. Patients in whom establishing an IV route of administration is difficult. The burn patient requiring repeated dressing changes. Patients requiring manipulative or diagnostic procedures. The debilitated patient. The emergency patient who may not have an empty stomach.

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

**SPECIAL NOTE**

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA-SHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

**CONTRAINDICATIONS**

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

**WARNINGS**

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemcially incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

***Usage in Pregnancy:*** Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

**PRECAUTIONS**

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. **The incidence of emergence reactions may be reduced** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with pre-anesthetic elevated cerebrospinal fluid pressure.

**ADVERSE REACTIONS**

*Cardiovascular:* Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

*Respiration:* Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

*Eye:* Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

*Psychological:* (See Special Note).

*Neurological:* In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

*Gastrointestinal:* Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

*General:* Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

**HOW SUPPLIED**

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15 – Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4581-12 – Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10
N 0071-4582-10 – Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10
N 0071-4585-08 – Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.

**SG**

**PARKE-DAVIS**

*PARKE-DAVIS*
*Division of Warner-Lambert Company*
*Morris Plains, NJ 07950*

©1979 Warner-Lambert Company

PD-JA-2645-1-P (4-79)

YOU KNOW THE POSITIVE SIDE OF NARCOTIC-SUPPLEMENTED ANESTHESIA...

TITRATES THE RESPIRATORY DEPRESSION OUT

# NARCAN®
## naloxone HCl
## NEUTRALIZES THE NEGATIVE

### NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

### Useful when narcotic/$N_2O$ anesthesia is employed

### Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism

The duration of activity of some narcotics may exceed that of NARCAN®. Observe the patient closely and give repeat doses of NARCAN® if needed.

### Also available, NARCAN® NEONATAL naloxone HCl

Please see next page for complete prescribing information.

**Endo Laboratories, Inc.**
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, New York 11530

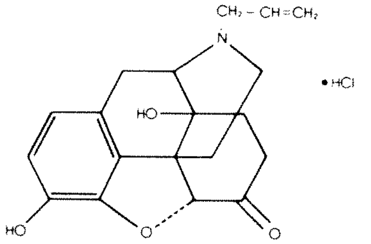
DU PONT
REG. U.S. PAT & TM OFF

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088

## OF NARCOTIC-SUPPLEMENTED ANESTHESIA

# NARCAN®
## naloxone HCl

**DESCRIPTION** NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

**ACTIONS** NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

**INDICATIONS** NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

**CONTRAINDICATIONS** NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

**WARNINGS** NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

**Usage in Pregnancy** Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

**PRECAUTIONS** In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

**ADVERSE REACTIONS** In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

**DOSAGE AND ADMINISTRATION** NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

**USAGE IN ADULTS Narcotic Overdose—Known or Suspected** The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

**Post Operative Narcotic Depression** For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

**USAGE IN CHILDREN Narcotic Overdose—Known or Suspected** The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

**USAGE IN NEONATES Narcotic-induced depression** The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

**HOW SUPPLIED** 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

**ANIMAL PHARMACOLOGY AND TOXICOLOGY** In the mouse and rat the intravenous $LD_{50}$ is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the $LD_{50}$ (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

**Endo Laboratories, Inc.**
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DU PONT

EDO-050N

May 1977

ELEVATORS
PERSONS UNDER AGE 14 ARE NOT PERMITTED ON PATIENT FLOORS WITHOUT SPECIAL PERMISSION

# Why your hospital needs a defibrillator on every floor.

All hospital elevators are notoriously slow. And with good reason, because in a hospital, the elevators are really freight elevators to move people and patients, equipment and supplies.

But when a life is ticking away, you can't afford to be waiting for the elevator. Will it come straight down? Or will it stop on another floor to pick up a patient on a gurney or to move on a food cart or to pick up linen or to transport visitors? Who knows? All you *really* know is that a life is ticking away and you're waiting for the elevator.

Considering what's at stake, and considering the relatively low cost of defibrillators, your hospital can't possibly make a wiser investment than installing an emergency cart on every floor. A *Physio-Control* emergency cart. *Topped* by a Physio-Control Lifepak 6 defibrillator/monitor. *Then* you're protected. And so are your people. And so are your patients.

The time to do it is *now.*

Only **Physio-Control**
makes the Lifepak.®

# THE WORLD IS ITS PROVING GROUND

**More widely investigated than any other inhalation anesthetic. Association with hepatotoxicity extremely rare.**[1]

Risk of liver toxicity from the use of FLUOTHANE® (halothane, U.S.P.) has been shown to be extremely rare. Unexplained jaundice following anesthesia with halothane "... was a rare occurrence (approximately 1:30,000 administrations) and ... the overall safety record of the anesthetic was excellent."[1]

These are conclusions drawn from the United States National Halothane Study, a comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE.

On the basis of postoperative morbidity for all types of operations, including high risk, the incidence for FLUOTHANE was 1.87%... compared with the 1.93% average for all anesthetic procedures.[2]*

**Over 450 million administrations worldwide.**

More anesthesiologists throughout the world choose FLUOTHANE more often than any other inhalation anesthetic. To date, there have been well over 110 million administrations in the United States alone... for a wide variety of procedures and techniques in patients of all ages.

**References:** 1. Brown, B.R. and Sipes, I.G.: Commentary-Biotransformation and hepatotoxicity of halothane. Biochem. Pharmacol. 26:2091, 1977. 2. Bunker, J.P. *et al*: The National Halothane Study, Washington, D.C. Government Printing Office, 1969.

# FLUOTHANE®

## (halothane, U.S.P.)

the most widely used inhalation anesthetic in the world

**Ayerst**®

**See following page for full prescribing information.*

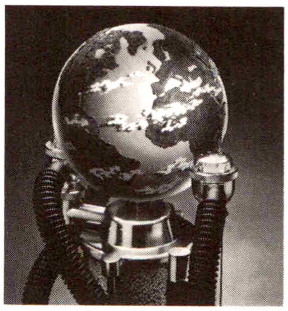
the most widely used inhalation anesthetic in the world

# FLUOTHANE®

BRAND OF

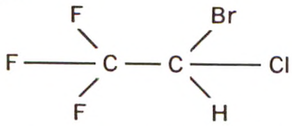
## halothane, U.S.P.

for patients of any age, in almost any kind of surgery



*(Complete text of package circular.)*

**Description.** FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

**Actions.** FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE (halothane, U.S.P.) is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

**Indications.** FLUOTHANE is indicated for the induction and maintenance of general anesthesia.

**Contraindications.** FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

**Warnings.** When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

*Usage in Pregnancy.* Safe use of FLUOTHANE (halothane, U.S.P.) has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

**Precautions.** The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

**Adverse Reactions.** The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

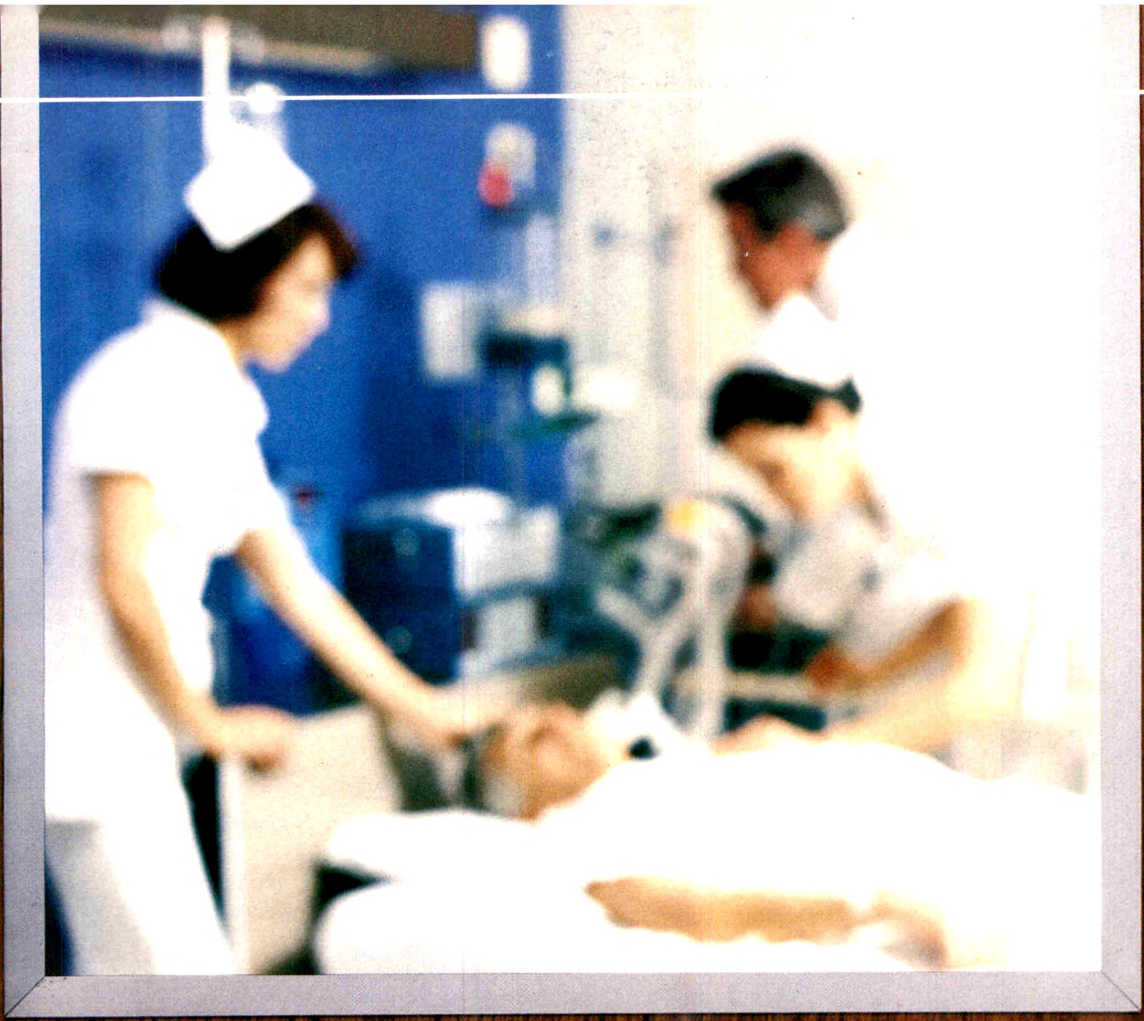
**Dosage and Administration.** FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

**How Supplied.** No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w).

**Ayerst**® Ayerst Laboratories
New York, N.Y. 10017

7918



# 1980.
# A NEW ERA OPENS IN CRITICAL CARE.

# The new CRITIKON

## The company totally committed to critical care.

**To create the new Critikon, Johnson & Johnson consolidated these established critical care names and product lines into one company:**

- **The complete product lines of Jelco Laboratories and Applied Medical Research.**
- **Blood/gas monitors from Critikon Division, McNeil Laboratories.**
- **I.V. infusion pumps and Lanz™ tracheal tubes from Extracorporeal Medical Specialties.**

This concentration on critical care medicine has some special benefits for you and your patients.

For instance, our sales force is now unified and expanded. Each representative now covers a smaller area, has more time to devote to your critical care needs, and is closer than before when you need quick service.

By combining our research teams, we can expand our R & D programs, develop new and better products, and improve cost effectiveness.

And we promise you this—we will service what we sell. If Critikon medical electronic equipment should need servicing, we will handle it on the spot or at one of our new regional service centers.

Bigger can mean better. And stronger. Better products and a stronger service capability for all of your needs. Critikon—our commitment is to critical care.

Write or call for more information: Critikon, Inc., P.O. Box 22800, Tampa, FL 33622. 800-526-3928 (In New Jersey: 201-524-2555.)

CRITIKON

010
5
extracorporeal
DINAMAP
074
121
092
068
DINAMAP
30

# Products to take some of the crisis out of critical care.

**Automated Blood Pressure Monitoring**

- DINAMAP® Noninvasive Blood Pressure Monitors and Recorders

**Continuous Blood/Gas Monitoring**

- OXYCHEK™ Oxygen Monitoring System
- OXYTRODE™ Arterial Monitoring System
- OXYTRAK™ Oxygen Analyzer
- OXYTRODE™ Sensor
- SENSOMAT™* III Continuous Oxygen Monitor

**Drug Administration Devices**

- JELCO® Disposable Syringes
- JELCO® Disposable Hypodermic Needles

**Vein/Artery Access Devices**

- JELCO® I.V. Catheter Placement Units
- JELCO® I.V. Catheter Placement Units with Syringe
- CATHLON IV® Catheter Placement Units
- JELCO® I.V. Catheter Kits
- JELCO® I.V. Prep and Care Kits
- JELCO® I.V. Stylet
- JELCO® Intermittent Injection Cap
- Long-Term Parenteral Alimentation Catheter (Scribner Type)

**Blood Collection Devices**

- JELCO® Blood Collection Needles

**Intravenous Fluid Management Devices**

- Model 2100 SIMPLICITY™ Infusion Pump
- HOLTER® Series Infusion Pumps
- I.V. Filters
- JELCO® Disposable Filter Needle
- JELCO® Disposable Filter Tube

**Temperature Monitoring**

- TEMP-A-STRIP® Brand Temperature Trend Indicator
- JELCO® Esophageal Multi-Probe II

**Airway Management Devices**

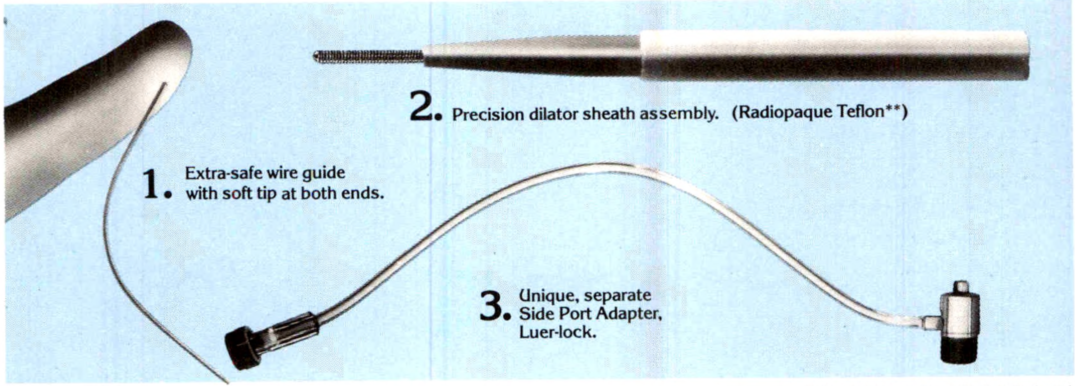
- LANZ™ Endotracheal Tubes
- LANZ™ Tracheostomy Tubes
- LANZ™ Tracheostomy Tubes with Inner Cannula

**CRITIKON**

**The Critical Care Company.**

P.O. Box 22800, 5041 West Cypress Street, Tampa, FL 33622 800-526-3928 (In N.J.: 201-524-2555)

# We've advanced percutaneous Swan-Ganz* catheterization with a safer way to navigate the body's central veins.


2. Precision dilator sheath assembly. (Radiopaque Teflon**)
1. Extra-safe wire guide with soft tip at both ends.
3. Unique, separate Side Port Adapter, Luer-lock.

*Edwards Laboratories **Du Pont Trademark

## With the first complete Percutaneous Sheath Introducer Kit to include a Side Port Adapter.

Arrow's goal is to increase patient safety every inch of the way. And in line with that goal, we've modified several of the components used in existing procedures. And combined them all in a series of precision-packed kits. The Percutaneous Sheath Introducer Kit with Side Port Catheter Adapter is one of them.

The kit contains a matched sheath-dilator assembly, either 6, 7, or 8 French. The 18 Ga. T.W. × 2½" introducer catheter easily passes the .035" × 40cm. spring wire guide, allowing the physician to utilize the internal jugular, subclavian, femoral or brachial veins.

The Arrow Side Port Adapter allows the introducer sheath to remain in the vessel with the catheter, resisting back-bleeding around the catheter. And provides the physician with an additional central line for I.V. continuous flushing or blood aspiration.

Each kit aggregates all components necessary for percutaneous catheterization procedures making it complete, ready and efficient when and where you need it.

This is yet another step towards Arrow's target of maximizing safety for you and your patients.

**The Percutaneous Sheath Introducer Kit with Side Port Catheter Adapter**

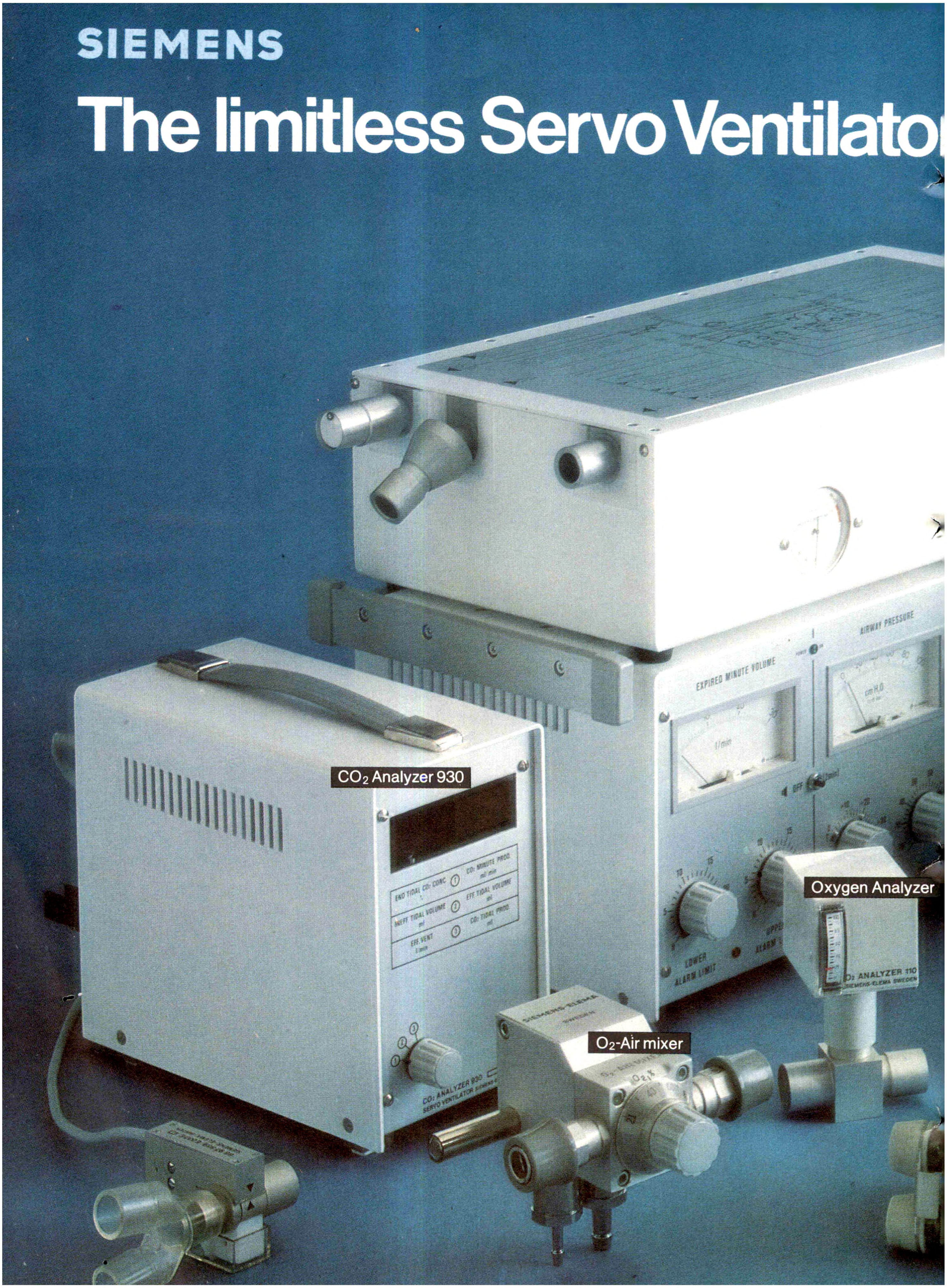
(for percutaneous catheter introduction of the internal jugular, subclavian, femoral or brachial veins).
Product No. AK-06600 (6 Fr.)
AK-06700 (7 Fr.)
AK-06800 (8 Fr.)

©1979 Arrow International

ARROW
INTERNATIONAL, INC.
Hill and George Avenues
Reading, Pennsylvania 19610
215-378-0131 • 800-523-8446

SIEMENS

The limitless Servo Ventilato



# System.

A complete system that has no limits for respiratory care and corresponds to the experienced clinician's entire capabilities.

The Servo Ventilator System provides instantaneous diagnostic possibilities through the $CO_2$ Analyzer and Lung Mechanics Calculator. The clinician can concentrate all his resources on immediate actions to save his patient, without restrictions or improvisations.

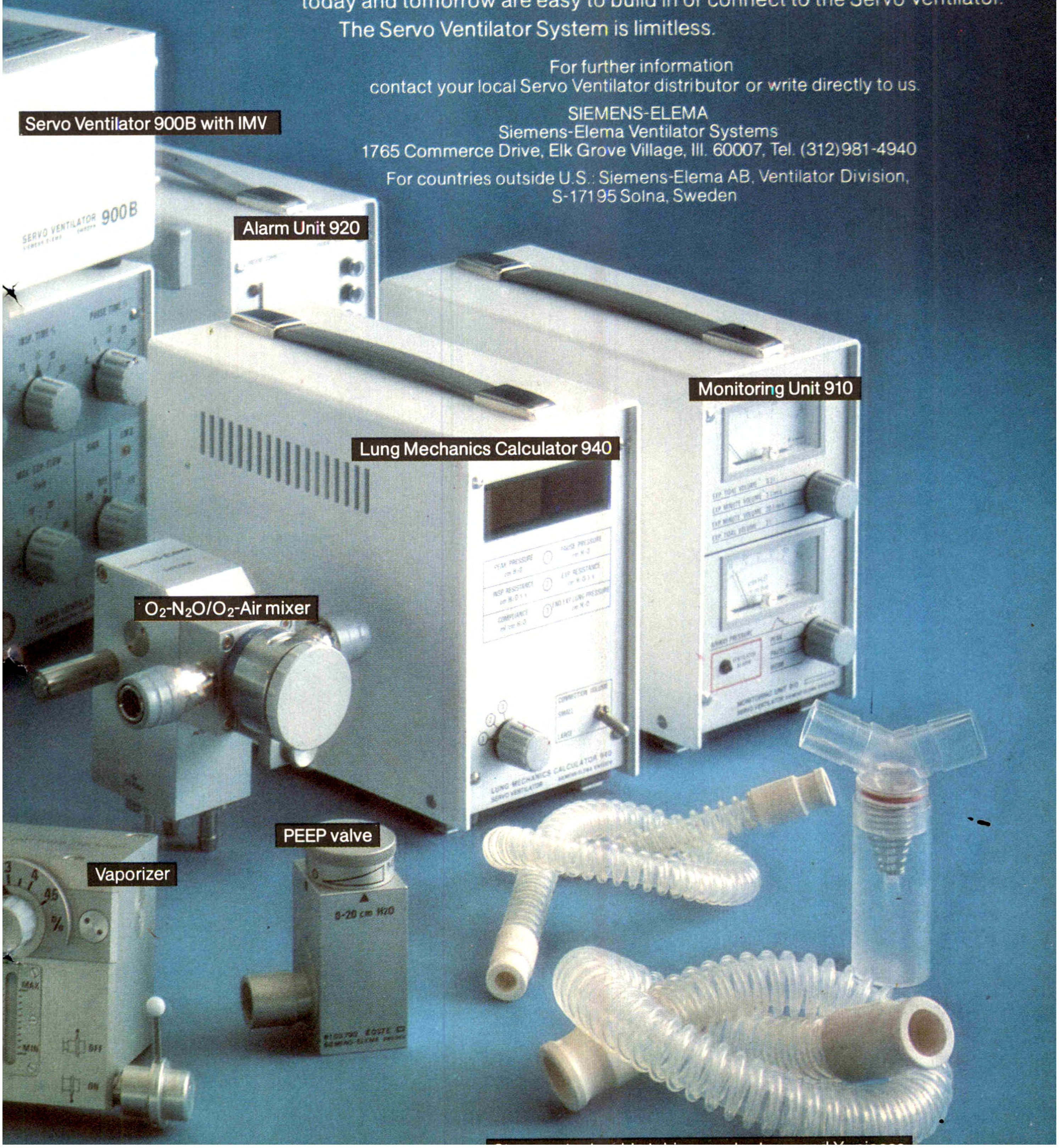
Thanks to the electronics, new devices developed from research of today and tomorrow are easy to build in or connect to the Servo Ventilator.

The Servo Ventilator System is limitless.

For further information
contact your local Servo Ventilator distributor or write directly to us.

SIEMENS-ELEMA
Siemens-Elema Ventilator Systems
1765 Commerce Drive, Elk Grove Village, Ill. 60007, Tel. (312) 981-4940

For countries outside U.S.: Siemens-Elema AB, Ventilator Division,
S-171 95 Solna, Sweden



See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

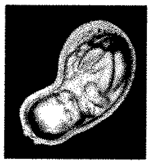
# More protection for the newborn

# Marcaine® hydrochloride

brand of

## bupivacaine hydrochloride

with or without epinephrine 1:200,000



**Indications:** Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

**Contraindication:** Marcaine is contraindicated in patients with known hypersensitivity to it.

**Warnings:** RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

*Usage in Pregnancy.* Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

**Precautions:** The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

**Adverse Reactions:** Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

*Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

*Treatment of Reactions.* Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

**References:**

1. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.
2. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
3. Scanlon JW, Ostheimer GW, Brown WV, et al: Neurobehavioral responses of newborns after maternal epidural anesthesia with bupivacaine. *Abstracts Annual Meeting, Soc. Obstet. Anesth. and Perinat.*, 1974.

BREON

**BREON LABORATORIES INC.**
90 Park Avenue, New York, N.Y. 10016

### FORMULA

| PRODUCT IDENTIFICATION | | | MULTIPLE DOSE VIAL | | | | | | SINGLE DOSE AMPUL | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marcaine HCl (brand of bupivacaine HCl) % | mg./ml. | Epinephrine* (as bitartrate) Dilution | Methylparaben mg./ml. | Sodium Bisulfite mg./ml. | Thioglycerol ml./ml. | Ascorbic Acid mg./ml. | 60% Sodium Lactate ml./ml. | Edetate Calcium Disodium mg./ml. | Sodium Bisulfite mg./ml. | Thioglycerol ml./ml. | Ascorbic Acid mg./ml. | 60% Sodium Lactate ml./ml. | Edetate Calcium Disodium mg./ml. |
| 0.25 | 2.5 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 0.25 | 2.5 | 1:200,000 | 1 | 0.5 | .001 | 2 | .0017 | 0.1 | .5 | .001 | 2 | .0017 | 0.1 |
| 0.5 | 5.0 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 0.5 | 5.0 | 1:200,000 | 1 | 0.5 | .001 | 2 | .0017 | 0.1 | .5 | .001 | 2 | .0017 | 0.1 |
| 0.75 | 7.5 | — | | | | | | | — | — | — | — | — |
| 0.75 | 7.5 | 1:200,000 | Not Available in Vials | | | | | | .5 | .001 | 2 | .0017 | 0.1 |

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved. Federal law prohibits dispensing without a prescription

More protection
for the newborn

A drug of choice for epidural
anesthesia that results in

- decreased placental transfer[1]
- fewer neurobehavioral changes than lidocaine or mepivacaine[2,3]

**Marcaine® hydrochloride**
brand of
**bupivacaine hydrochloride**
with or without epinephrine 1:200,000
See adjacent page for prescribing information. Not recommended for paracervical block.
Model by Hubbard Scientific Co. Northbrook, Ill.

# *Anesthesia and Analgesia*

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | 4 | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | 4 | 5 | 6 |
| 36 | 1957 | – | 2 | 3 | – | – | 6 | 44 | 1965 | – | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | 3 | 4 | 5 | 6 |
| 38 | 1959 | 1 | 2 | 3 | 4 | 5 | 6 | 46 | 1967 | – | 2 | 3 | 4 | 5 | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | 2 | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | 3 | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | 4 | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | 2 | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | 3 | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 |
| 59 | 1980 | 1 | | | | | |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.
BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955
OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.
Ten-Year (1960-1969) Cumulative Index—$3.00.
Ten-Year (1970-1979) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122
Please send me the publications circled above, or listed hereunder:

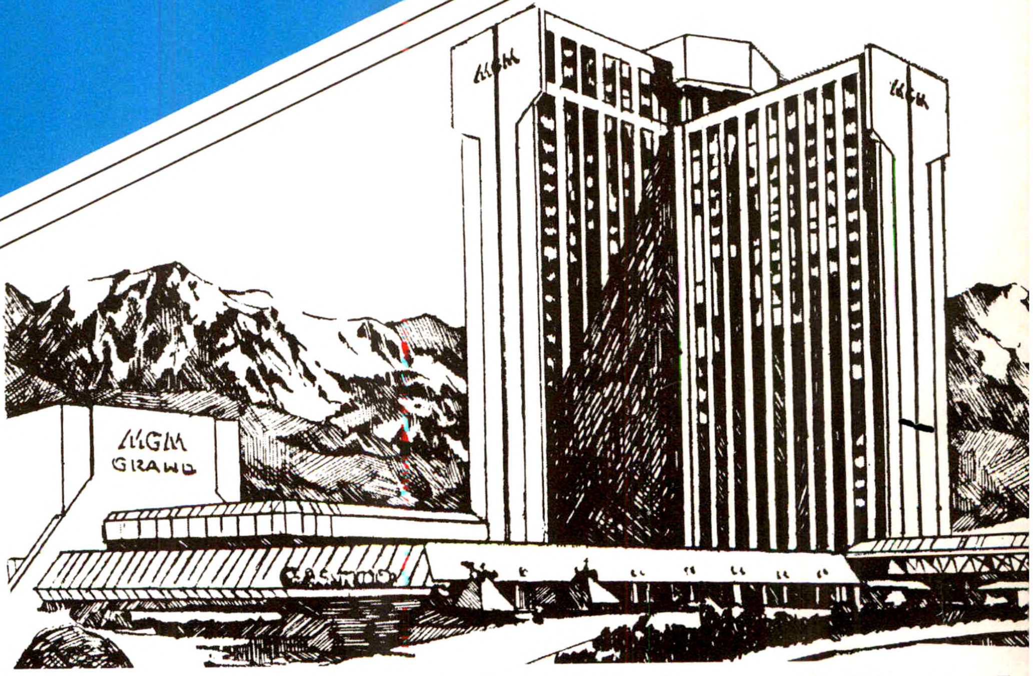
☐ Check for $______ enclosed.
☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name ______________________________
Address ______________________________
City, State, Zip ______________________________

# 54th Congress

March 9-13, 1980

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY



## MGM Grand Hotel
## Reno, Nevada

## 54th CONGRESS MEETING SCHEDULE

*SUNDAY, MARCH 9th:*

Registration: 1–7 p.m.
Exhibits: 1–5 p.m.
"The Keys of Paradise" (NOVA movie on endorphins): 3–4 p.m.
Complimentary Informal Reception: 6–7 p.m.

*MONDAY, MARCH 10th through THURSDAY, MARCH 13th:*

*Registration:* Daily, coinciding with scientific meeting hours.

*Scientific Program:* Monday: 8:30–4:30 p.m.
Tuesday: 8 a.m.–4:30 p.m.
Wednesday: 8 a.m.–12 Noon (FREE AFTERNOON)
Thursday: 8 a.m.–4:15 p.m.

...A total of 62 scientific papers and 16 Review Course Lectures will be offered in concurrent sessions throughout the 3½ day scientific meeting.

...The Becton-Dickinson and Baxter/Travenol Lectures will be given at single sessions at 1:30 p.m. on Monday and Tuesday.

(NOTE: A booklet including the 16 Review Course Lectures and abstracts of the 62 papers will be given to attendees as part of their registration. After the meeting this will be available for sale to others through the Cleveland business office at $5 per copy.)

*Scientific and Technical Exhibits:* In addition to the Sunday exhibit viewing hours, exhibits will be open from 10 a.m. to 5 p.m. on Monday and Tuesday; and from 8 a.m. to 12 noon on Wednesday.

## REGISTRATION FEES

| | *Paid by March 3* | *At Meeting* |
|---|---|---|
| IARS Members, Associate Members | $75.00 | $85.00 |
| IARS Educational Members | NO FEE | NO FEE |
| Non-Members | $125.00 | $135.00 |
| * New Members | $100.00 | $110.00 |
| ** Non-Members (residents, nurse trainees) | $20.00 | $20.00 |
| *** New Members (residents, nurse trainees) | $30.00/$45.00 | $30.00/$45.00 |

* with membership application
** with letter from program director
*** with completed application; $30 for 2-yr., $45 for 3-yr. membership

## CONTINUING EDUCATION CREDITS

**American Medical Association:** This Continuing Medical Education offering meets the criteria for 22 hours of Category 1 credit for the Physicians Recognition Award of the A.M.A.

**American Association of Nurse Anesthetists:** Prior approval pending for 22 AANA continuing education credits.

## PRE-REGISTRATION MATERIAL, HOTEL CARD, PROGRAM

Registration material will be sent in mid-December to all IARS members, associate members and educational members.

IARS members and others outside of the United States who wish to attend the meeting should advise Cleveland office so that another set of material can be sent airmail.

# EDITORIAL

# The World Federation of Societies of Anesthesiologists and You

A LITTLE less than 30 years ago a small group of far-sighted anesthesiologists conceived of an organization that would include all the anesthesiologists of the world through their respective national societies. At that time it was felt that although many anesthesia societies existed around the world, the creation of an international organization would hasten the development of our specialty and raise the prestige of anesthesiologists to a greater degree than would be possible through the efforts of the individual national societies alone. Since membership is by societies, not by individuals, the formation of national societies would therefore be encouraged. Thus was the World Federation of Societies of Anesthesiologists born.

In furtherance of its grand objective, official relations with the United Nations through its main medical arm, the World Health Organization, were solicited and subsequently ratified. The World Federation of Societies of Anesthesiologists now participates in all the deliberations of the various regional meetings of the World Health Organization and its advice concerning worldwide problems in anesthesiology is heard.

One of the most important consequences of these official relations with the World Health Organization has been the development of two anesthesia training centers—one in Caracas, Venezuela and one in Manila, The Philippines. Direct assistance in terms of fellowships, visiting consultantships, and material aid has come from the World Health Organization. This assistance, combined with the support of the World Federation of Societies of Anesthesiologists and other organizations, has resulted in the training of a respectable number of anesthesiologists from the Third World. Other centers are being planned in Africa and West Asia.

Equally as important has been the establishment of a direct link between the national societies in many countries with their governments. Membership in the World Federation of Societies of Anesthesiologists has given national societies the opportunity to negotiate directly with their Ministries of Health in resolving problems, not only of scientific nature but also of political nature. All this has led to progress for our specialty, especially in the countries of the Third World.

There is need for more communication, however. The general membership of some of the largest societies in the Federation is apparently uninformed about the Federation and its objectives in spite of the fact that these societies have been represented in the hierarchy of the Federation for many years. This is regrettable because the large societies are in a unique position to help the small, struggling societies in more ways than one.

The World Federation of Societies of Anesthesiologists has sponsored six World Congresses and 18 Regional Congresses in the last 24 years. The Regional Congresses take place in between the World Congresses with the result that international anesthesia congresses under the auspices of the World Federation of Societies of Anesthesiologists take place around the world every 2 years. No doubt communication and interaction among anesthesiologists has been enhanced by these meetings. In the very near future a Visitors' Exchange Training Program will commence wherein two well-known American anesthesiologists will be invited by three Latin-American countries to give lectures and demonstrations and, it is hoped, to gain a greater insight into the status of our specialty in those countries. The World Federation of Societies of Anesthesiologists invites all who are interested in this type of project to give their support.

There is a growing demand for a more continuous form of communication such as a newsletter which would be circulated worldwide. This newsletter would contain items of interest, both scientific and nonscientific, and thus would stimulate closer cooperation among the member societies. This is one area in which more affluent societies could give support beyond the mere payment of annual dues.

Anesthesiology today is in a period of transition—a transition that demands correct decisions on the part of its leaders due to the widening gap between the scientific advances in our field and the safe delivery of anesthesia to the individual patient—a transition that will determine whether or not anesthesiology will continue to be a distinct medical specialty in the future or will become a "fossil of history."

The World Federation of Societies of Anesthesiologists stands for safe anesthesia for all the people of the world. The need is critical and may never be adequately filled but as long as the World Federation of Societies of Anesthesiologists exists every possible effort will be made to accomplish this objective. The World Federation is you and you are the World Federation.

Quintin J. Gomez, MD
*President, World Federation of Societies of Anesthesiologists*
*Department of Anesthesiology*
*Philippine General Hospital*
*Manila, The Philippines*

ANESTH ANALG
59:89–92, 1980

# Obesity and the Cephalad Spread of Analgesia following Epidural Administration of Bupivacaine for Cesarean Section

**Robert Hodgkinson, MA, MD,* and Farkhanda J. Husain, MD†**

HODGKINSON, R., AND HUSAIN, F. J.: Obesity and the cephalad spread of analgesia following epidural administration of bupivacaine for cesarean section. Anesth Analg 59:89–92, 1980.

Epidural anesthesia using 20 ml of 0.75% bupivacaine at L3-4 with the patient in the left lateral position and the table horizontal was employed for cesarean section in 147 A.S.A. class 1 or 2 parturients under the age of 35 with a single fetus. The height of the analgesia was positively correlated with the body mass index (BMI) (weight in kilograms divided by the height in square meters), a measure of adiposity, and with body weight. Both correlations were statistically significant ($p < 0.001$). There was no statistically significant correlation with the patients' height or age. It is concluded that higher levels of epidural block should be anticipated in obese obstetrical patients in proportion to their obesity. Twenty milliliters of 0.75% bupivacaine must frequently be augmented to provide adequate analgesia for cesarean section in thin parturients (BMI below 28) whereas it is too high a dosage for obese patients.

**Key Words:** ANESTHETIC TECHNIQUES: epidural; COMPLICATIONS: obesity.

BROMAGE[1] describes five factors affecting physical spread of local anesthetics within the epidural space but emphasizes that some of them frequently correlate poorly with segmental spread of analgesia. Height is negatively correlated with spread while age is positively correlated. The upright position is associated with less cephalad spread and rapid injection produces more extensive analgesia. Increased segmental spread is associated with diabetes and arteriosclerosis.

The object of this study was to define factors such as the patients' height and obesity which may affect the cephalad spread of analgesia following injection into the lumbar epidural space of a fixed dose of local anesthetic for cesarean section. The dose was 20 ml of 0.75% bupivacaine, which is within the recommended dose of 18 to 20 ml described by Albright[2] for epidural anesthesia for cesarean section. We have been using 20 ml of 0.75% bupivacaine for this purpose for several years preceding this study. Since sensory analgesia to T4-6 is required for cesarean section, a fixed dose of 20 ml corresponds to a standard dose of 1.1 ml per segment.

To divide the population into the obese and the nonobese, like dividing it into the hypertensive and normotensive,[3] is to create an artefact. Similarly, to define obesity is to create an artefact. Obesity like hypertension is a quantitative disease with quantitative consequences. The degree of obesity can be described in terms of body mass index (BMI) both conveniently and accurately. Keys et al[4] found that the BMI (weight in kilograms divided by height in square meters) was superior to the ponderal index ($3\sqrt{\text{weight/height}}$) or weight/cubic height in the

---

* Associate Professor, Departments of Anesthesiology, Obstetrics and Gynecology.

† Assistant Professor, Department of Anesthesiology.

Received from the Department of Anesthesiology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284. Accepted for publication September 17, 1979.

Reprint requests to Dr. Hodgkinson.

quantitation of obesity. BMI increases with increasing obesity unlike the ponderal index, which decreases. The BMI and the sum of skinfold thickness measurements have approximately the same correlation to body density measurements[5] which are the most accurate[6, 7] but also a most difficult and laborious method of estimating the proportion of fat in the body. The sum of skinfold thicknesses was not used in this study not only because it did not offer an advantage in accuracy, but also because skin calipers are not usually available in anesthetic practice, whereas the patients' weight and height are readily available. This study used the weight of each parturient at term; on the average this weight would be 11 kg over her nonpregnant weight. To orientate the reader unfamiliar with BMI, a patient 152.4 cm (60") in height weighing 63.5 kg (140 lb) and a person 183 cm (72" tall) weighing 90.7 kg (200 lb) both have a BMI of approximately 27. A convenient table for BMI has been published.[8]

## Methods and Materials

All 147 patients were A.S.A. physical status 1 or 2, term parturients undergoing either elective or emergency cesarean section. They were placed in the left lateral position with the operating table maintained in a horizontal position for 40 minutes following the administration of epidural anesthesia. The L3-4 interspace was identified and a 17-gauge Tuohy needle was introduced into the epidural space. With the bevel pointing cephalad, 20 ml of 0.75% bupivacaine without epinephrine was injected in 40 seconds. A catheter was then inserted and the patient turned to the supine position with a wedge under the right hip to produce left uterine displacement and the table tilted to the left at a 15° angle. The patient was examined at 5-, 10-, 15-, 20-, and 30-minute intervals during anesthesia and surgery and again at the completion of the operation for loss of pinprick sensation along both midaxillary lines using the stylette from the epidural needle. When the level of the block was higher on the left side, due to the administration of the epidural in the left lateral position, a mean was taken of the right and left side to describe the level of the block.

Statistical analyses included chi-square, simple linear regression, correlation coefficients, and finally, stepwise regression analysis.[9] Chi-square was used as a simple, rapid test of the effect of the four predictor variables (BMI, height, weight, and age) on the level of the block obtained. Its calculation also provided a check on the more complicated parametric analyses that followed. Regression analysis and a Student's $t$-test of the regression slope against zero provided a more graphic and detailed analysis. Correlation coefficients show the interrelationship between the predictor variables and the level of the sensory block as a function of time. A regression analysis was performed to predict the final outcome (i.e., final height of the segmental sensory block) using a stepwise multiple correlation technique. In this method the predictor that had the highest product-momentum correlation with the final height of the segmental sensory block was drawn from the rest of the variables and used to compute a regression analysis equation. The variance attributable to a particular variable was separated from the remaining variables by partial correlation. That is, the influence of the variable was determined while the influence of other variables was held constant. In the next step, the variable with the next highest partial correlation to the final outcome was selected and entered in a new regression analysis. The variance attributable to the first two variables was calculated while holding the influence of the remaining variables constant. The steps continued until no further significant independent variables were included in the regression analysis. F ratios were calculated at each step and if the probability of the ratio was greater than 0.05 it was removed from the equation.

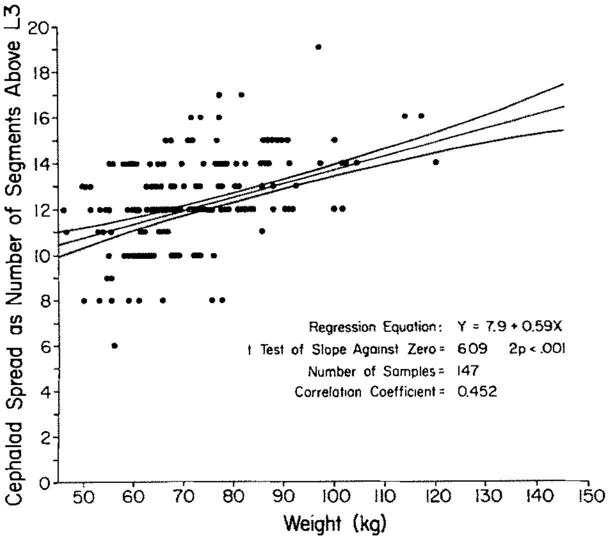


FIG 1. Relationship of parturients' weight to the highest point of cephalad spread of analgesia as determined by pinprick following a single injection at L3/L4 of 20 ml of 0.75% bupivacaine. Three lines on the graph represent the regression line with 95% confidence limits to the population drawn on either side.

## Results

A chi-square analysis of the data showed that there was an association between the cephalad spread of analgesia and the patient's BMI ($p < 0.001$). The contingency table was drawn with the cephalad spread described as below 11, T9-11, T7-8, T5-6, and T4 and above, and the BMI classified as below 25, 25–, 30–, and above 35. A similar contingency table for weight also showed an association between cephalad spread and weight ($p < 0.001$). No statistically significant relationship existed between the height of the anesthesia and patients' height or age. These findings were confirmed by regression analysis (Figs 1 and 2). Testing the regression slope against zero by a Student's *t*-test showed the relationships between height of sensory block and weight or BMI to be statistically significant ($p < 0.001$).

The interrelationship of the four predictor variables and the relationship between these and the cephalad spread of the block with time can be seen in the correlation coefficients between them (Table 1). Taller patients are more likely to be heavy ($R = 0.5$, $p < 0.01$) and weight tends to increase with age ($R = 0.27$, $p < 0.01$). The increase in weight with age may account for the greater cephalad spread with age ($R = 0.2$, $p < 0.05$). The largest component of BMI is weight ($R = 0.89$); height contributes less ($R = 0.11$). The level of anesthesia shows an increasingly large correlation coefficient with respect to BMI and weight as time from the induction of anesthesia increases. It ultimately reaches $R = 0.53$ for BMI and 0.45 for weight.

Used as a predictor of the level of sensory block ultimately reached, sensory levels at 5 minutes ($R = 0.39$) and 10 minutes ($R = 0.57$) have a lower or almost the same correlation coefficient as BMI ($R = 0.53$). The latter is information available before the epidural injection is given; the former becomes available only during the anesthesia. Table 2 summarizes the results of stepwise regression analyses. One variable, BMI predicts the ultimate level of sensory anesthesia ($p < 0.01$). It contributes 27.9% of the variance. Addition of the other three predictors (height, weight, and age) increase the predictability of the level of sensory anesthesia by only 1%.

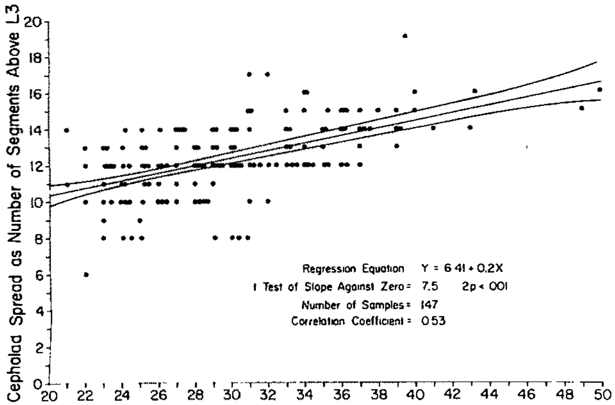


FIG 2. Relationship of parturients' body mass index (BMI) to the highest point of cephalad spread of analgesia as determined by pinprick following a single injection at L3/L4 of 20 ml of 0.75% bupivacaine. Three lines on the graph represent the regression line with 95% confidence limits to the population drawn on either side.

**TABLE 2**

**Analysis of Contribution of the Four Predictor Variables (BMI, Age, Weight, and Height) to Final Outcome (Height of Sensory Block) by Stepwise Progression**

| Variable entered | Multiple R | Increase in prediction | F |
|---|---|---|---|
| BMI | 0.52875 | 0.27957 | 56 270* |
| Age | 0.53687 | 0.00866 | 1 751† |
| Weight | 0.54003 | 0.00340 | 0 686† |
| Height | 0.540.4 | 0.00013 | 0 026† |

* $p < 0.01$.
† Not significant.

**TABLE 1**

**Correlation Coefficients Between the Four Predictor Variables and Level of Sensory Block as a Function of Time**

| | Predictor variables | | | | Sensory block level at: | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | BMI | Weight | Height | Age | 5 min | 10 min | 15 min | 20 min | Time of highest level |
| BMI | 1.0 | 0.89 | −0.11 | 0.20 | 0.18 | 0.25 | 0.27 | 0.43 | 0.53 |
| Weight | | 1.00 | 0.50 | 0.27 | 0.10 | 0.12 | 0.17 | 0.35 | 0.45 |
| Height | | | 1.00 | 0.03 | −0.04 | −0.15 | −0.11 | −0.01 | −0.04 |
| Age | | | | 1.00 | 0.09 | 0.10 | 0.11 | 0.17 | 0.20 |
| 5 min | | | | | 1.00 | 0.69 | 0.53 | 0.43 | 0.39 |
| 10 min | | | | | | 1.00 | 0.82 | 0.65 | 0.57 |
| 15 min | | | | | | | 1.00 | 0.86 | 0.74 |
| 20 min | | | | | | | | 1.00 | 0.89 |

Thirteen of 48 parturients with a BMI below 28 or a weight below 73 kg had to have the block augmented at 30 minutes. None of the patients with a BMI above 28 or a weight above 73 kg had inadequate anesthesia.

## Discussion

Many dosage schedules are used for epidural analgesia for cesarean section. Many rely upon height and age.[2] The patients' height in this study showed low correlation with the cephalad spread and was statistically not significant. Age within the range of 18–35 years showed a slight statistically insignificant relationship with cephalad spread. The modest relationship seen was probably due to the increase of weight with age. The levels of analgesia 5 and 10 minutes after injection of local anesthetic into the epidural space are also often used clinically to predict the final level of anesthesia. Frequently the patient is tilted into a Trendelenburg position if the 5- and 10-minute levels of anesthesia are low. Neither of these two levels of anesthesia was found to be as reliable as BMI (a value available before the block is initiated) in predicting the final level of analgesia. Eight obese patients (BMI 30 or above) had a T9 or lower levels of anesthesia at 10 minutes but had achieved a T4 level at 30 minutes. Tilting these patients would probably have resulted in a very high level.

Despite levels of sensory analgesia to C5 in some parturients, respiration was not embarrassed. Systolic blood pressure decreased to below 100 torr in only 12% of patients and ephedrine, 10 to 20 mg, was administered to only 3%. Initially, we were concerned that decreases in blood pressure were being missed, but checking cuff pressures with a Dynamap showed no discrepancies. The low incidence of hypotension is attributed to absence of narcotic premedication, use of a Crawford wedge, a 15° lateral tilt of the table, and rapid infusion of lactated Ringer's solution through two 14-gauge needles if systolic blood pressure decreased more than 10 torr.

The fact that 15% of patients showed increasing cephalad spread of the block 30 minutes after injection is noteworthy. Bupivacaine continues to anesthetize additional segments for up to 1 hour in some patients. In a rare case this could lead to respiratory embarrassment. It is important to monitor the level throughout the operation and after transfer to the recovery room.

### REFERENCES

1. Bromage PR: Epidural Anesthesia. Philadelphia, WB Saunders Co, 1978, pp 135–139
2. Albright GA: Anesthesia in Obstetrics. First edition. Menlo Park, Addison-Wesley Publishing Co, 1978, p 274
3. Pickering G: Therapeutics, art or science? JAMA 242:649–653, 1979
4. Keys A, Aravanis C, Blackburn H, et al: Coronary heart disease: overweight and obesity as risk factors. Ann Intern Med 77:15–27, 1972
5. Keys A, Fidanza F, Karvonen MJ, et al: Indices of relative weight and obesity. J Chronic Dis 25:329–343, 1972
6. Behnke AR, Feen BG, Welham WC: Specific gravity of healthy man. JAMA 118:495–498, 1942.
7. Siri WE: The gross composition of the body, in Advances in Biological and Medical Physics. Edited by JH Lawrence, CA Tobias. New York, Academic Press, 1956, Vol 4, pp 239–280
8. Bray GA, Jordan HA, Sims EAH: Evaluation of the obese patient: 1. An agoritham. JAMA 235:1487–1491, 1976
9. Draper N, Smith H: Applied Regression Analysis. New York, John Wiley & Sons, Inc, 1966

ANESTH ANALG
59:93-99, 1980

# Cardiovascular Responses to Nitrous Oxide Exposure for Two Hours in Man

**Ryohei Kawamura, MD,* Theodore H. Stanley, MD,† John B. English, MD,* Gary E. Hill, MD,* Wen-Shin Liu, MD,* and Lynn R. Webster, MD‡**

KAWAMURA, R., STANLEY, T. H., ENGLISH, J. B., HILL, G. E., LIU, W.-S., AND WEBSTER, L. R.: Cardiovascular responses to nitrous oxide exposure for two hours in man. Anesth Analg 59: 93-99, 1980

Cardiovascular responses to increasing (20, 40, and 60%) concentrations of nitrous oxide or nitrogen in oxygen for 15 minutes as well as responses to 2 hours of exposure to 60% nitrous oxide or nitrogen in oxygen were determined and compared in 30 healthy, supine, untrained volunteers who received no other drugs or medications. No concentration of nitrogen produced a significant change in any cardiovascular variable measured, nor did 20 and 40% $N_2O$. Sixty percent nitrous oxide for 15 minutes significantly increased $Pa_{CO_2}$, heart rate, stroke volume, cardiac output, mean arterial blood pressure, and central venous pressure. Inhalation of 60% nitrogen also produced no significant change in any cardiovascular variable. In contrast, inhalation of nitrous oxide for 2 hours transiently increased arterial blood pressure (at 15 minutes), heart rate (at 15 and 30 minutes), stroke volume (at 15, 30, and 45 minutes) and decreased systemic vascular resistance (at 15 minutes). Cardiac output significantly increased for the 1st hour of exposure to 60% nitrous oxide but returned to values similar to control (room air) during the 2nd hour. Prolonged inhalation of nitrous oxide resulted in a constant increase in $Pa_{CO_2}$ and progressive but mild decreases in arterial pH and calculated base deficit but no change in dead space/tidal volume ratios. These findings demonstrate that nitrous oxide stimulates the cardiovascular system in supine, healthy, untrained volunteers but that the stimulation is transient. The data suggest that early stimulation of the cardiovascular system during nitrous oxide breathing may be related to central nervous system excitation secondary to incomplete anesthesia and/or an increase in $Pa_{CO_2}$.

**Key Words:** ANESTHETICS, Gases: nitrous oxide; HEART: nitrous oxide.

FOR MANY years nitrous oxide was thought to exert little influence on cardiovascular dynamics.[1, 2] A number of reports[3–11] suggest that this may not be so. This study investigates the cardiovascular effects of increasing concentrations of nitrous oxide for brief (15 minutes) periods of time as well as the effect of 2 hours of administration of a single, high concentration (60% in oxygen) of the gas in untrained, healthy volunteers.

## Methods

This study was approved by the University of Utah Human Experimentation Committee. The experimental subjects were 30 healthy (weight 60 to 80 kg), young (aged 21 to 25 years), untrained, adult male volunteers. Written informed consent was obtained 1 to 3 days prior to the experiment.

Upon arrival in the experimental laboratory in the morning, each volunteer was placed on an operating room stretcher. Room temperature was maintained at

---

* Assistant Professor of Anesthesiology.
† Professor of Anesthesiology/Surgery.
‡ Research Fellow in Anesthesiology.
Received from the Department of Anesthesiology, The University of Utah College of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132.
Reprint requests to Dr. Stanley.

72 F and the volunteers were covered with a single sheet after preparatory procedures were completed. Catheters were then placed percutaneously into a central vein and, via the radial artery, into the central aorta. The aortic catheter was attached to a computer substation module. After appropriate calibration, computer analysis of the aortic pulse-pressure curve, as described by Warner and co-workers,[12] was used for measurement of cardiac output, stroke volume, heart rate, mean aortic blood pressure, and systemic vascular resistance. The accuracy of this technique has recently been confirmed in this laboratory.[13] An infusion of 5% dextrose in Ringer's solution was begun at a rate of 400 ml/hr through the central venous catheter.

After obtaining control data, while breathing room air, six volunteers (group 1A) were given 20% nitrogen in oxygen to breathe through an air-tight anesthesia face mask attached to a semiclosed anesthesia circle system for 15 minutes. Nitrogen in oxygen was supplied to the circle system via a previously calibrated Bird nitrogen blender at a rate of 5 L/min. The nitrogen concentration was then increased to 40% and after 15 minutes data were recollected. Following this, nitrogen concentration was increased to 60% in oxygen and data were collected again. The volunteers then breathed room air for 15 minutes and after this, 20, 40, and 60% concentrations of nitrous oxide in oxygen were administered for 15 minutes each via a previously calibrated Bird nitrous oxide blender as during nitrogen and oxygen breathing. Data were collected and arterial blood samples analyzed for $Pa_{CO_2}$, $Pa_{O_2}$, and pH and base deficit on a Radiometer ABL-acid-base machine, 15 minutes after each change in nitrogen or nitrous oxide concentration. In a similar fashion, six additional volunteers (group 1B) were first given increasing concentrations of nitrous oxide and then increasing concentrations of nitrogen. Results from groups 1A and 1B were similar irrespective of the sequence of nitrogen and nitrous oxide administration; therefore, all data were combined.

The remaining 18 volunteers (group 2) were divided into three subgroups of six patients each. One subgroup was given 60% nitrous oxide in oxygen to breathe via a face mask and semiclosed circle system for 2 hours followed by 60% nitrogen in oxygen for an additional 2 hours. Cardiovascular data were recorded immediately before, 15 minutes after, and every 15 minutes during the 4 hours of nitrous oxide and nitrogen breathing. Arterial blood samples for $Pa_{CO_2}$, $Pa_{O_2}$, and pH analysis were obtained immediately before each data collection period. A second subgroup was treated in the same fashion except they breathed 60% nitrogen in oxygen during the first 2 hours and 60% nitrous oxide in oxygen during the latter 2 hours. A third subgroup was treated in the same fashion as the second except that the mask was attached to a non-rebreathing system employing Collins 3-cm i.d. inspiratory and expiratory jay valves. In this group mixed expiratory gases were collected in 50-L Douglas bags every 15 minutes and dead space/tidal volume ratios were calibrated using the equation: dead space/tidal volume = $Pa_{CO_2}$ − mixed expired $P_{CO_2}/Pa_{CO_2}$. Since the cardiovascular data from the three subgroups in group 2 were similar irrespective of the sequence of nitrous oxide and nitrogen breathing, cardiovascular and blood gas data were combined. Body temperature was not measured during the study in order to avoid disturbing the volunteers. However, oral temperature was measured in three patients in group 1A and three in group 1B at the conclusion of the study.

Data were analyzed for statistical significance using Student's paired *t*-test; $p < 0.05$ was considered statistically significant.

## Results

Volunteers in group 1 exposed to increasing concentrations of nitrogen showed the expected significant ($p < 0.01$) increase in $Pa_{O_2}$ with 20% nitrogen in oxygen which decreased as higher concentrations of nitrogen were breathed (Table 1). Arterial pH and $Pa_{CO_2}$ were not changed by any concentration of nitrogen in group 1 volunteers but pH was reduced and $Pa_{CO_2}$ increased by exposure to 60% nitrous oxide. Volunteers in group 1 exposed to increasing concentrations of nitrous oxide had changes in $Pa_{O_2}$ similar to those observed in volunteers exposed to nitrogen at comparable concentrations of the two gases. None of the six patients in group 1 who had oral temperatures measured at the conclusion of the study had a temperature above 37.8 C or below 37.5 C.

No cardiovascular variable measured was significantly altered by breathing any concentration of nitrogen in group 1 volunteers (Table 2). In contrast, 60% nitrous oxide produced significant increases in stroke volume, cardiac output, and central venous pressure when compared to either room-air values or values obtained during breathing of 60% nitrogen. Heart rate and mean aortic blood pressure were not changed by any concentrations of nitrous oxide.

**TABLE 1**

**Aortic Blood Gas and pH Changes during 15-Minute Exposures to Increasing Concentrations of Nitrous Oxide or Nitrogen in Oxygen (mean ± SD)***

| | Room air | Nitrogen in oxygen and partial pressure (torr) | | | Room air | Nitrous oxide and partial pressure (torr) | | |
|---|---|---|---|---|---|---|---|---|
| | | 20% (128) | 40% (256) | 60% (384) | | 20% (128) | 40% (256) | 60% (384) |
| $Pa_{O_2}$ (torr) | 85 ± 4 | 389 ± 18† | 196 ± 11† | 149 ± 10† | 84 ± 3 | 400 ± 14† | 209 ± 10† | 147 ± 9† |
| $Pa_{CO_2}$ (torr) | 32 ± 2 | 32 ± 2 | 32 ± 2 | 32 ± 2 | 32 ± 2 | 34 ± 2 | 35 ± 2 | 36 ± 3§,‖ |
| pH | 7.40 ± 0.02 | 7.40 ± 0.02 | 7.40 ± 0.02 | 7.39 ± 0.02 | 7.40 ± 0.02 | 7.40 ± 0.02 | 7.38 ± 0.02 | 7.37 ± 0.02§ |
| Base deficit (meq/L) | 0.7 ± 0.8 | 0.8 ± 0.6 | 0.7 ± 0.8 | 0.9 ± 0.7 | 0.8 ± 0.8 | 1.1 ± 0.8 | 1.7 ± 0.9 | 1.9 ± 0.7 |

* Average barometric pressure in Salt Lake City during the performance of these studies was 640 torr.

† $p < 0.01$, Student's paired *t*-test when compared to room-air values.

§ $p < 0.05$, Student's paired *t*-test when compared to room-air values.

‖ $p < 0.05$ Student's paired *t*-test when compared to 60% $N_2$ values.

**TABLE 2**

**Cardiovascular Responses to 15-Minute Exposures to Increasing Concentrations of Nitrous Oxide or Nitrogen in Oxygen (mean + SD)***

| | Room air | Nitrogen in oxygen and partial pressure (torr) | | | Room air | Nitrous oxide and partial pressure (torr) | | |
|---|---|---|---|---|---|---|---|---|
| | | 20% (128) | 40% (256) | 60% (384) | | 20% (128) | 40% (256) | 60% (384) |
| Heart rate (beats/min) | 61 ± 9 | 58 ± 7 | 66 ± 8 | 67 ± 8 | 62 ± 8 | 65 ± 7 | 67 ± 9 | 69 ± 6 |
| Stroke volume (ml) | 73 ± 7 | 76 ± 5 | 75 ± 6 | 72 ± 6 | 71 ± 6 | 72 ± 5 | 79 ± 6 | 79 ± 7§,‖ |
| Cardiac output (L/min) | 4.7 ± 0.4 | 5.1 ± 0.6 | 5.0 ± 0.4 | 4.7 ± 0.5 | 4.6 ± 0.4 | 4.7 ± 0.4 | 5.2 ± 0.3 | 5.4 ± 0.5‡,‖ |
| Mean blood pressure (torr) | 87 ± 11 | 88 ± 9 | 88 ± 10 | 85 ± 10 | 88 ± 9 | 88 ± 10 | 86 ± 9 | 87 ± 8 |
| Central venous pressure (torr) | 8 ± 2 | 7 ± 2 | 8 ± 1 | 8 ± 2 | 6 ± 1 | 8 ± 2 | 10 ± 2§ | 11 ± 3§,‖ |
| Systemic vascular resistance (PRU) | 22 ± 2 | 21 ± 3 | 21 ± 2 | 23 ± 2 | 21 ± 2 | 19 ± 1 | 17 ± 2 | 18 ± 2 |

* Average barometric pressure in Salt Lake City during the performance of these studies was 640 torr.

‡ $p < 0.025$, Student's paired *t*-test when compared to room-air values.

§ $p < 0.05$, Student's paired *t*-test when compared to room-air values.

‖ $p < 0.05$, Student's paired *t*-test when compared to 60% $N_2$ values.

Volunteers in group 2 exposed to 60% nitrogen for 2 hours sustained an increase in $Pa_{O_2}$ throughout this period but experienced no significant change in $Pa_{CO_2}$, mixed expired $P_{CO_2}$, calculated base deficit, or dead space/tidal volume ratio (Table 3). Arterial pH decreased slightly during the 2nd hour of exposure to nitrogen; however, this change was not statistically significant. Group 2 volunteers exposed to 60% nitrous oxide had increases in $Pa_{O_2}$ similar to those observed in subjects exposed to nitrogen. However, in contrast to the latter, those breathing nitrous oxide showed a significant increase in $Pa_{CO_2}$, a similar though not statistically significant increase in mixed expired $P_{CO_2}$, and an earlier onset of and a more prolonged and significant reduction in arterial pH. Calculated base deficit was significantly increased after 105 to 130 minutes of exposure to 60% nitrous oxide but was unchanged during exposure to nitrogen. Neither nitrogen nor nitrous oxide significantly altered dead space/tidal volume ratios at any time during the experiment. Blood gas and pH values returned to values similar to original room-air control values within 15 minutes of breathing room air after both nitrous oxide and nitrogen were discontinued after 2 hours.

Two hours of breathing of 60% nitrogen did not significantly alter any cardiovascular variable measured at any time (Table 4). However, breathing 60% nitrous oxide transiently increased mean aortic blood pressure (at 15 minutes), heart rate (at 15 and 30 minutes), and stroke volume (at 15, 30, and 45 minutes) and decreased systemic vascular resistance (at 15 minutes), when compared either to values obtained while breathing room-air controls or to values obtained during breathing of 60% nitrogen for the same time. Cardiac output increased significantly during the first 60 minutes of nitrous oxide exposure. The peak increases in cardiac output occurred at 15 and 30 minutes. Following this, cardiac output gradually decreased toward room air values. Nitrous oxide did

**TABLE 3**

**Aortic Blood Gas and pH Changes during 2-Hour Exposures to 60% (384 Torr) Nitrous Oxide or 60% (384 Torr) Nitrogen in Oxygen (mean ± SD)**

| | Room air | Minutes of 60% $N_2O$ or 60% $N_2$ | | | | | | | | Room air |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 15 | 30 | 45 | 60 | 75 | 90 | 105 | 120 | |
| $Pa_{O_2}$ (torr) | | | | | | | | | | |
| $N_2O$ | 84 ± 5 | 140 ± 8‡ | 144 ± 8‡ | 146 ± 6‡ | 151 ± 6‡ | 147 ± 6‡ | 147 ± 6‡ | 150 ± 7‡ | 149 ± 6‡ | 85 ± 11 |
| $N_2$ | 84 ± 5 | 139 ± 9‡ | 146 ± 6‡ | 150 ± 7‡ | 149 ± 7‡ | 148 ± 6‡ | 150 ± 6‡ | 147 ± 7‡ | 147 ± 7‡ | 87 ± 9 |
| $Pa_{CO_2}$ (torr) | | | | | | | | | | |
| $N_2O$ | 32 ± 1 | 34 ± 2 | 36 ± 2§,‖ | 36 ± 2§,‖ | 36 ± 2§,‖ | 36 ± 2§,‖ | 36 ± 2§,‖ | 36 ± 2§,‖ | 36 ± 2§,‖ | 31 ± 3 |
| $N_2$ | 32 ± 2 | 32 ± 2 | 32 ± 2 | 32 ± 2 | 32 ± 2 | 31 ± 2 | 32 ± 2 | 32 ± 2 | 32 ± 2 | 32 ± 2 |
| pH | | | | | | | | | | |
| $N_2O$ | 7.40 ± 0.02 | 7.38 ± 0.02 | 7.37 ± 0.01 | 7.36 ± 0.01 | 7.35 ± 0.01 | 7.34 ± 0.01§,‖ | 7.34 ± 0.02§,‖ | 7.34 ± 0.02§,‖ | 7.32 ± 0.02§,‖ | 7.44 ± 0.02 |
| $N_2$ | 7.41 ± 0.02 | 7.41 ± 0.02 | 7.41 ± 0.02 | 7.42 ± 0.03 | 7.41 ± 0.02 | 7.40 ± 0.02 | 7.39 ± 0.01 | 7.39 ± 0.01 | 7.39 ± 0.02 | 7.40 ± 0.02 |
| Base deficit (meq) | | | | | | | | | | |
| $N_2O$ | 0.7 ± 0.7 | 0.9 ± 0.9 | 1.4 ± 1.0 | 1.7 ± 1.0 | 2.0 ± 1.0 | 2.2 ± 0.9 | 2.2 ± 1.1 | 2.3 ± 0.6‡ | 2.5 ± 0.6‡ | 1.4 ± 1.0 |
| $N_2$ | 0.4 ± 1.2 | 0.5 ± 0.9 | 0.5 ± 0.9 | 0.5 ± 0.8 | 0.6 ± 0.9 | 0.7 ± 1.1 | 0.8 ± 1.2 | 0.8 ± 1.1 | 0.8 ± 1.0 | 0.9 ± 0.7 |

‡ $p < 0.025$, Student's paired *t*-test when compared to original room-air values.
§ $p < 0.05$, Student's paired *t*-test when compared to original room-air values.
‖ $p < 0.05$, Student's paired *t*-test when compared to $N_2$ values at the same period of time.

**TABLE 4**

**Cardiovascular Responses to 2-Hour Exposures to 60% (384 Torr) Nitrous Oxide or 60% (384 Torr) Nitrogen in Oxygen (mean ± SD)**

| | Room air | Minutes of 60% $N_2O$ or 60% $N_2$ | | | | | | | | Room air |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 15 | 30 | 45 | 60 | 75 | 90 | 105 | 120 | |
| Heart rate (beats/min) | | | | | | | | | | |
| $N_2O$ | 74 ± 9 | 84 ± 7§,‖ | 83 ± 7§,‖ | 81 ± 8 | 80 ± 8 | 78 ± 9 | 77 ± 8 | 74 ± 7 | 75 ± 8 | 73 ± 9 |
| $N_2$ | 73 ± 7 | 75 ± 7 | 77 ± 8 | 75 ± 8 | 76 ± 9 | 74 ± 8 | 74 ± 8 | 73 ± 7 | 71 ± 6 | 72 ± 7 |
| Stroke vol (ml) | | | | | | | | | | |
| $N_2O$ | 58 ± 7 | 66 ± 7§,‖ | 66 ± 7§,‖ | 65 ± 8§,‖ | 63 ± 8 | 63 ± 7 | 64 ± 7 | 64 ± 7 | 63 ± 7 | 56 ± 7 |
| $N_2$ | 56 ± 7 | 56 ± 6 | 55 ± 7 | 55 ± 7 | 57 ± 8 | 57 ± 7 | 57 ± 8 | 56 ± 8 | 57 ± 7 | 57 ± 7 |
| Cardiac output (L/min) | | | | | | | | | | |
| $N_2O$ | 4.3 ± 0.4 | 5.5 ± 5†,‖ | 5.5 ± 0.4†,‖ | 5.3 ± 0.4†,‖ | 5.0 ± 0.4§,‖ | 4.9 ± 0.3 | 4.9 ± 0.3 | 4.7 ± 0.4 | 4.7 ± 0.3 | 4.2 ± 0.5 |
| $N_2$ | 4.2 ± 5 | 4.2 ± 5 | 4.2 ± 0.4 | 4.1 ± 0.5 | 4.3 ± 0.4 | 4.3 ± 0.3 | 4.2 ± 0.3 | 4.2 ± 0.3 | 4.2 ± 0.2 | 4.1 ± 0.3 |
| Mean blood pressure (torr) | | | | | | | | | | |
| $N_2O$ | 92 ± 8 | 105 ± 6§,‖ | 100 ± 7 | 99 ± 8 | 96 ± 9 | 100 ± 7 | 98 ± 8 | 99 ± 7 | 100 ± 7 | 91 ± 6 |
| $N_2$ | 92 ± 7 | 97 ± 7 | 93 ± 6 | 93 ± 7 | 93 ± 6 | 98 ± 6 | 98 ± 6 | 96 ± 6 | 97 ± 8 | 96 ± 9 |
| Central venous pressure (torr) | | | | | | | | | | |
| $N_2O$ | 5 ± 2 | 8 ± 2 | 7 ± 2 | 5 ± 2 | 6 ± 2 | 6 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 |
| $N_2$ | 5 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 | 5 ± 2 | 6 ± 2 | 5 ± 2 |
| Systemic vascular resistance (PRU) | | | | | | | | | | |
| $N_2O$ | 20.2 ± 2.2 | 17.1 ± 1.8§,‖ | 18.0 ± 1.8 | 17.6 ± 2.0 | 18.0 ± 2.2 | 19.1 ± 2.3 | 19.0 ± 2.0 | 19.4 ± 1.9 | 19.6 ± 1.6 | 20.4 ± 1.9 |
| $N_2$ | 20.9 ± 2.0 | 21.7 ± 1.0 | 21.1 ± 1.6 | 20.6 ± 2.0 | 20.5 ± 2.0 | 21.6 ± 1.8 | 22.1 ± 2.1 | 22.7 ± 2.4 | 22.7 ± 1.8 | 21.2 ± 1.7 |

† $p < 0.025$, Student's paired *t*-test when compared to original room-air values.
§ $p < 0.05$, Student's paired *t*-test when compared to original room-air values.
‖ $p < 0.05$, Student's paired *t*-test when compared to nitrogen values at the same period of time.

not alter central venous pressure at any time in group 2 volunteers.

Three of 12 volunteers in group 1 lost consciousness with 60% nitrous oxide. One of this group also became nauseated and vomited during breathing 40% nitrous oxide. (When vomiting occurred, the anesthesia face mask was removed and only replaced after vomiting stopped. Data were not recorded until the volunteer had breathed nitrous oxide for 15 minutes following an episode of vomiting.) All subjects sweated and had dilated pupils during 60% nitrous oxide.

None of the subjects in group 2 became nauseated or vomited during nitrogen breathing but nine of 18 subjects became nauseated or vomited during nitrous oxide inhalation. The nausea never occurred before 20 minutes of nitrous oxide inhalation and was usually over in a few minutes. However, one volunteer, who was not included in the study, was continually sick and the experiment was discontinued after 1 hour of nitrous oxide inhalation. All group 2 volunteers began sweating and most had dilated pupils within 15 minutes of initiation of nitrous oxide inhalation. These signs of central nervous system excitement disappeared 30 minutes later. Four of the volunteers in group 2 lost consciousness at some time during their 2-hour exposure to 50% nitrous oxide. No group 2 volunteers exposed to nitrogen sweated or had dilated pupils.

## Discussion

In spite of the wide popularity and long history of use of nitrous oxide in anesthesia, the cardiovascular effects of breathing nitrous oxide alone have been carefully studied in only a few reports,[3-5, 11, 14] and data from these reports are conflicting. Thus, while some have shown that nitrous oxide has no effect on myocardial mechanics[14] and cardiovascular dynamics,[15] others have found that the gas depresses myocardial contractility[4, 5, 15] and cardiovascular dynamics.[3-5] Still other investigators have demonstrated that cardiovascular stimulation can also occur during nitrous oxide inhalation.[3, 11] Possible reasons for these conflicting findings include, as previously discussed[11, 16]: the variety of protocols and experimentatal subjects used; the presence of myocardial pathology (coronary artery disease); the presence or absence of preexisting anxiety and heightened sympathetic activity; changes in arterial blood gases and pH secondary to nitrous oxide inhalation; and the simultaneous use of either other compounds or anesthetics, or intubation with or without positive pressure respiration. The results of the present study demonstrate that in unpremedicated, untrained, supine, healthy volunteers, high concentrations of nitrous oxide produce cardiovascular stimulation which gradually disappears with prolonged continued inhalation of the gas. The data suggest that early stimulation of the cardiovascular system during nitrous oxide breathing may be related to central nervous system excitation secondary to incomplete anesthesia and/or an increase in $Pa_{CO_2}$. The data also suggest that with continued breathing of the gas adaption occurs or a mild acidosis may inhibit early cardiovascular stimulation.

Increases in $Pa_{CO_2}$ with nitrous oxide inhalation have been demonstrated when the gas is breathed alone,[5, 11] or when it is added to the inspired mixture of gases of subjects anesthetized and mechanically ventilated with a potent inhalational anesthetic and oxygen.[17] Since nitrous oxide increases tidal and minute volumes and does not influence the responses to hypercarbia in subjects not anesthetized with another anesthetic,[11, 18] respiratory depression is not an adequate explanation for the increases in $Pa_{CO_2}$ that accompany its use. Other mechanisms that have been suggested as possible explanations for the increase in $Pa_{CO_2}$ that occurs during nitrous oxide breathing include the second gas effect of nitrous oxide on alveolar carbon dioxide tension ($PA_{CO_2}$)[19] and an increase in physiologic dead space.[11, 19] Although a concentrating effect of nitrous oxide in $PA_{CO_2}$ has been described,[19] this phenomenon should only last for a short period of time. Therefore, it is unlikely that this mechanism is responsible for the 3- to 4-torr increase in $Pa_{CO_2}$ which was found in group 2 volunteers after 1 to 2 hours of inhalation of 60% nitrous oxide. Our data in this study indicate that nitrous oxide does not influence dead space/tidal volume ratios in spontaneously breathing man. It was not possible to measure carefully tidal volume in this study, but the bag in the circle system on the anesthesia machine seemed to empty to a greater degree during nitrous oxide breathing in all patients. Previous investigations[11, 18] have demonstrated that nitrous oxide increases tidal volume. If nitrous oxide did indeed increase tidal volume in this study, then physiologic dead space must also have been increased for the dead space/tidal volume ratio to remain unchanged.

Increases in $Pa_{CO_2}$ are known to increase heart rate, stroke volume, and cardiac output, and reduce systemic vascular resistance.[20, 21] Cullen and co-workers[21] showed that cardiac output increases approximately 5% for each torr increase in $Pa_{CO_2}$ when $Pa_{CO_2}$ is raised from normal resting levels to 50 to 55 torr in unanesthetized volunteers breathing hypercarbic gas mixtures. Volunteers in the present study had $Pa_{CO_2}$ values close to normal for this altitude (33 to 34 torr) during control conditions. Increases in $Pa_{CO_2}$ and cardiac output observed in group 1 volunteers and after 30 and 45 minutes in group 2 in this study are consistent with the findings of Cullen et al.[21]

Cardiovascular stimulation during nitrous oxide breathing might also be explained by central nervous system excitation secondary to partial or incomplete anesthesia and/or to increased circulating catecholamine concentrations. The excitement state associated with inductions of diethyl ether anesthesia, is accompanied by both of the above.[22] Eisele and Smith[5] found that trained volunteers given 40% nitrous oxide to breathe experienced significant increases in plasma norepinephrine and, to a lesser extent, plasma epinephrine. The peak increases in both these amines occurred after 15 minutes of nitrous oxide inhalation. After 45 minutes of nitrous oxide both norepinephrine and epinephrine plasma levels began returning toward room air (control) values. Why plasma catecholamines became elevated during early exposure to nitrous oxide and returned to control levels with continued breathing of the gas in Eisele and Smith's study is unknown but this suggests that time of exposure is important. Similar changes in circulating catecholamines in our subjects could explain both the rapid early cardiovascular stimulation and subsequent return of cardiovascular dynamics to control values as well as the sweating and pupillary dilation in group 2 volunteers. Absence of increases in mean arterial blood pressure and heart rate during inhalation of 50% nitrous oxide in group 1 in contrast to group 2 and greater increases in cardiac output after 15 minutes of exposure to 60% nitrous oxide in group 2 than in group 1 are additional evidence that time of exposure to nitrous oxide influences cardiovascular changes observed.

Whereas nausea and vomiting might also explain some of the cardiovascular stimulation observed during nitrous oxide breathing in this study, they probably are not important causes. The reasons for this are that only one of the 12 volunteers in group 1 complained of nausea and vomiting during inhalation of 60% nitrous oxide yet all experienced stimulation of cardiovascular dynamics. Although 50% of group 2 volunteers became nauseated or vomited this never occurred before 20 minutes when cardiovascular stimulation was not only already present but usually maximal. Furthermore, nausea and vomiting usually were over in a few minutes while some evidence of cardiovascular stimulation was most often present for an additional 20 to 30 minutes. Finally, there appeared to be no difference in the degree of heart rate, stroke volume, arterial blood pressure, and cardiac output increases in volunteers who became nauseated and vomited or those that did not.

An alternative mechanism that could explain the initial stimulation and subsequent return of cardiovascular dynamics to control values with continued inhalation of nitrous oxide in group 2 volunteers is the initial respiratory acidosis and following mixed respiratory and metabolic acidosis. This was less impressive but was also seen in group 1 volunteers. Lunn and co-workers[11] found similar changes in pH when increasing concentrations of nitrous oxide were given to calves over a 3-hour period. Since respiratory acidosis alone causes significant increases in stroke volume, heart rate, and cardiac output while metabolic acidosis or mixed metabolic and respiratory acidosis depresses the cardiovascular system during anesthesia with certain anesthetics,[20] return of cardiovascular dynamics to control values with continued nitrous oxide inhalation may be due to the negative inotropic and chronotopic effects of an increasing metabolic acidosis. The reason why continued nitrous oxide inhalation results in a mild but increasing metabolic acidosis over the relatively short period of 2 hours in spite of adequate hydration and dextrose administration, is unclear from our data.

## REFERENCES

1. Feldman EJ, Ridley RW, Wood EH: Hemodynamic studies during thiopental sodium and nitrous oxide anesthesia in humans. Anesthesiology 16:463–489, 1955
2. Heller ML, Watson TR, Storrs RC: Analgesia with nitrous oxide-oxygen-curare for major surgery in the poor risk patient. JAMA 161:1534–1542, 1956
3. Craythorne NWB, Darby TD: The cardiovascular effects of nitrous oxide in the dog. Br J Anaesth 37:560–565, 1965
4. Eisele JH, Trenchard D, Stubb J, et al: The immediate cardiac depresson by anaesthetics in conscious dogs. Br J Anaesth 41: 86–93, 1969
5. Eisele JH, Smith NT: Cardiovascular effects of 40% nitrous oxide in man. Anesth Analg 51:956–961, 1972
6. Hornbein TF, Martin WE, Bonica JJ, et al: Nitrous oxide effects on the circulatory and ventilatory responses to halothane. Anesthesiology 31: 250–260, 1969
7. Smith NT, Eger EI II, Stoelting RK, et al: The cardiovascular and sympathetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410–421, 1970
8. Smith NT, Eger EI II, Gregory GA, et al: The cardiovascular responses to the addition of nitrous oxide to fluroxene in man. Br J Anaesth 44:142–148, 1972
9. McDermott RW, Stanley TH: The cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 41:89–91, 1974
10. Lappas DG, Buckley MJ, Laver MB, et al: Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary-artery surgery. Anesthesiology 43:61–69, 1975
11. Lunn JK, Liu WS, Stanley TH, et al: Peripheral and cardiac

effects of nitrous oxide in the bovine. Can Anaesth Soc J 24: 571–585, 1977
12. Warner HR, Gardner RM, Toronto AT: Computer based monitoring of cardiovascular functions in postoperative patients. Circulation (Suppl II) 38:1168–1174, 1968
13. English JB, Hodges MR, Sentker C, et al: Comparison of aortic pulse wave contour analysis and thermodilution methods of measuring cardiac output during anesthesia in the dog. Anesthesiology, in press 1980
14. Goldberg AH, Sohn YZ, Phear WPC: Direct myocardial effects of nitrous oxide. Anesthesiology 37:373–380, 1972
15. Lundborg RO, Milde JH, Theye RA: Effect of nitrous oxide on myocardial contractility of dogs. Can Anaesth Soc J 13:361–367, 1966
16. Eisele JH, Reiton JA, Masumi RA, et al: Myocardial performance and $N_2O$ analgesia in coronary-artery disease. Anesthesiology 44:16–20, 1976
17. Smith NT, Eger EI II, Stoelting RK, et al: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410–421, 1970
18. Eckenhoff JE, Helrich M: The effect of narcotics, thiopental and nitrous oxide upon response to hypercapnia. Anesthesiology 19:240–253, 1958
19. Kitahata AM, Taub A, Conte AJ: The effect of nitrous oxide on alveolar carbon dioxide tension: a second gas effect. Anesthesiology 35:607–611, 1971
20. Carson SAA, Chorley GE, Hamilton FN, et al: Variation in cardiac output with acid-base changes in the anesthetized dog. J Appl Physiol 20:948–95, 1965
21. Cullen DJ, Eger EI II, Gregory GA: The cardiovascular effects of carbon dioxide in man, conscious and during cyclopropane anesthesia. Anesthesiology 31:407–413, 1969
22. Black GW, McArdle L, McCullough H, et al: Circulating catecholamines and some cardiovascular, respiratory, metabolic and pupillary responses during diethyl ether anesthesia 24: 168–179, 1969

---

## Extracorporeal Membrane Oxygenation

Nine medical centers collaborated in a prospective randomized study to assess the role of prolonged extracorporeal membrane oxygenation (ECMO) in the therapy for severe acute respiratory failure (ARF). Ninety adult patients were selected by a uniform clinical protocol and treated with either conventional mechanical ventilation (48 patients) or mechanical ventilation supplemented with partial venoarterial bypass (42 patients). Four patients in each group survived. The majority of patients suffered acute bacterial or viral pneumonia (57%). All nine patients with pulmonary embolism and six patients with posttraumatic respiratory failure died. The majority of patients died of progressive reduction of transpulmonary gas exchange and decreased compliance due to diffuse pulmonary inflammation, necrosis, and fibrosis. The data demonstrate that ECMO supported respiratory gas exchange but did not increase the probability of long-term survival in patients with severe ARF. (*Zapol WM, Snider MT, Hill JD, et al: Extracorporeal membrane oxygenation in severe acute respiratory failure. JAMA 242:2193–2196, 1979*)

ANESTH ANALG
59:100-102, 1980

# A Weak Negative Inotropic Effect of Protamine Sulfate upon the Isolated Canine Heart Muscle

**Naofumi Iwatsuki, MD, PhD,* Shuh Matsukawa, MD,† and Kenichi Iwatsuki, MD, PhD‡**

---

IWATSUKI, N., MATSUKAWA, S., AND IWATSUKI, K.: A weak negative inotropic effect of protamine sulfate upon the isolated canine heart muscle. Anesth Analg 59:100–102, 1980.

The direct effect of protamine sulfate upon myocardial inotropism was studied using an isolated canine heart muscle preparation. Isometric force (*F*) was decreased to 87.6 ± 1.2% of control values by a concentration of $50 \times 10^{-3}$ g/L protamine, which is approximately equal to the estimated serum concentration of protamine when administered clinically in doses of 4 mg/kg. The decrease in *F* was accompanied by a decrease in the maximum velocity of force development (*dF/dt*) but no alteration in time to peak force. Administration of the preservative of protamine sulfate did not alter *F* and *dF/dt*. This suggests that protamine produces a direct negative inotropic effect, mediated by a decrease in intensity but not by a decrease in duration of the active state.

**Key Words:** HEART: contractility; BLOOD, Coagulation: protamine.

---

SYSTEMIC hypotension may occur following the intravenous administration of protamine sulfate. Direct vasodilating effects of protamine have been offered as an explanation for this hypotension, but the effect of protamine upon myocardial inotropism remains controversial.[1, 2] In the intact heart, myocardial performance is likely to be influenced by changes in pre-load and after-load, and by changes in neurohumoral compensatory mechanisms, as well as by changes in inotropism. We, therefore, measured the direct effect of protamine sulfate upon myocardial inotropism using isolated canine heart muscle preparation.

## Methods and Materials

Trabeculae from the right ventricle were excised rapidly from adult dogs, weighing 6 to 8 kg, anesthetized with thiopental (25 mg/kg IV). The excised muscle was suspended vertically in an experimental bath filled with Krebs-Henseleit solution kept at 30 C by a surrounding thermobath and bubbled with a gas mixture of 95% $O_2$-5% $CO_2$. The composition of the bathing solution (millimolar per liter) was as follows: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 21, $KH_2PO_4$ 1.2, and glucose 5.6. The pH of the bathing solution bubbled with the gas mixture ranged from 7.32–7.40.

A lower end of the muscle was clamped by a specially made clip and was fixed on the bottom of the experimental bath. The upper end of the muscle was also clipped and was connected to an isometric force transducer (Shinkoh UL-100-230) through a steel wire. Electrical stimulation at a frequency of 12/min was applied by mass electrodes placed parallel to the muscle with an intensity of 15 to 20% above threshold and a duration of 5 msec (Nihon Kohden MSE-3).

The muscle was allowed to contract isometrically for more than 60 minutes until a stable contraction was obtained. The muscle was then elongated to a length at which isometric force reached maximum

---

* Assistant Professor, Tohoku University School of Medicine.
† Assistant, Tohoku University School of Medicine.
‡ Professor, Dokkyo Medical School; Professor Emeritus, Tohoku University School of Medicine.

Received from the Department of Anesthesiology, Tohoku University School of Medicine, 1-1 Seiryo-cho, Sendai 980, Japan. Accepted for publication October 1, 1979.

Reprint requests to Dr. Iwatsuki.

(*L*max). All measurements were done at *L*max. Isometric force was recorded by a direct writing recorder (Nihon Kohden WL-260-M). The muscle length was measured with a telescope (Pika PPM-2) placed in front of the muscle bath.

The concentration of protamine sulfate (Shimizu Seiyaku Co, Ltd) used in this study was 1 w/v% with 0.25 w/v% phenol as a preservative; its pH is 4.7–6.7. The concentration of protamine in the bathing solution was increased stepwise by adding protamine sulfate directly to the bathing solution (40 ml) in amounts of 0.05, 0.05, and 0.1 ml, respectively.

Each heart muscle served as its own control. The data were analyzed statistically by Student's *t*-test for paired data; *p* values less than 0.05 were considered statistically significant.

Muscle length, blotted weight, and cross-sectional area of the six trabeculae used for this study were 5.93 ± 1.79 mm, 2.7 ± 1.2 mg, and 0.46 ± 0.12 $mm^2$ (mean ± SD), respectively.

## Results

Administration of protamine sulfate to the bathing solution produced an initial transient increase followed by a gradual decrease in isometric force (*F*) with *F* then becoming stable about 5 to 7 minutes later (Fig 1). *F* decreased to 87.6 ± 1.2% (mean ± SE) of the control value and the maximum velocity of isometric force development (*dF/dt*) was 85.2 ± 1.4% of the control at a concentration of $50 \times 10^{-3}$ g/L of protamine (Fig 2). The time to peak force from the onset of contraction (*TPF*) was unchanged by protamine (Fig 2). Normalized values of *F* and *dF/dt* by the cross-sectional area of the muscle are shown in the Table.

Following administration of 6.25 and $12.5 \times 10^{-3}$ g/L of phenol *F* averaged 103.8 ± 1.3% and 102.8 ± 2.9%, respectively, and *dF/dt* averaged 103.7 ± 1.7% and 102.4 ± 1.5% of the control value, respectively. These values were not statistically significantly different from the control values; 6.25 and $12.5 \times 10^{-3}$ g/L are the concentrations of the preservative in 25.0 and $50.0 \times 10^{-3}$ g/L of protamine sulfate, respectively.

The depression in *F* and *dF/dt* produced by protamine were easily counteracted by the administration of $CaCl_2$, 30 mg (5 mM), or epinephrine, 1 μg ($2.5 \times 10^{-5}$ g/L) (Fig 1).

Protamine is given after heparin in clinical use, but protamine, when mixed with heparin, produces a white precipitate, therefore the effects of protamine together with heparin were not studied in this experiment.

## Discussion

The present study demonstrates that protamine sulfate produces a dose-related direct negative inotropic effect, which is expressed by a decrease both in isometric force (*F*) and in the maximum velocity of force development (*dF/dt*).

Previous reports on the direct effects of protamine upon myocardial inotropism have been conflicting.

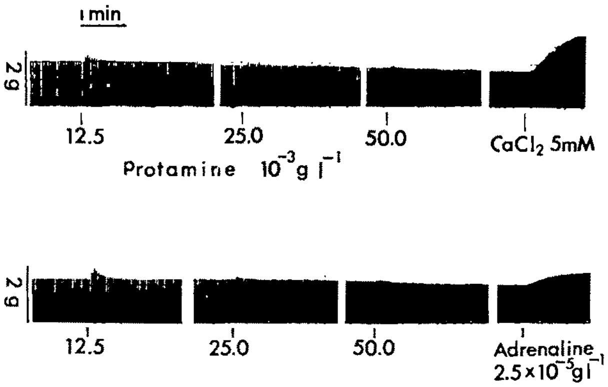


FIG 1. Changes in isometric force associated with administration of protamine sulfate, together with responses to $CaCl_2$ and epinephrine. Concentrations represent total concentration in the bathing solution, thus the amount of protamine added to the bathing solution (40 ml) at each time was 0.5 mg, 0.5 mg, and 1.0 mg, respectively; the amount of $CaCl_2$ added was 30 mg, and the amount of epinephrine was 1 μg.

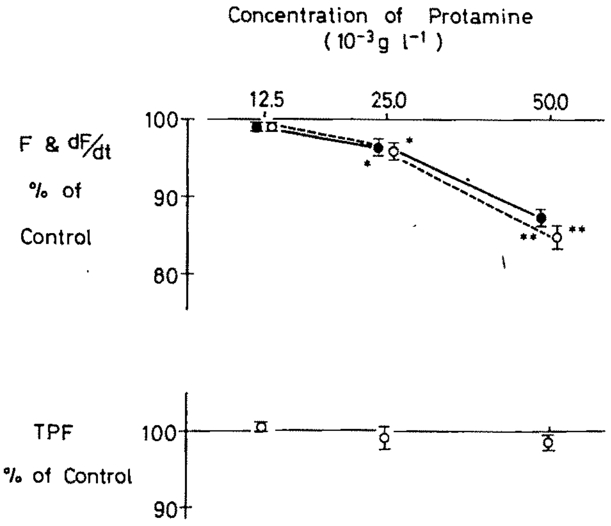


FIG 2. Percent changes in isometric force (*F*), the maximum velocity of force development (*dF/dt*) and the time to peak force from the onset of contraction (*TPF*) associated with administration of various concentrations of protamine. The concentration of protamine on the abscissa is plotted on a logarithmic scale. The percent changes in *F*, *dF/dt*, and *TPF* on the ordinate are expressed as means ± SE; ●——● = *F*; O- - -O = *dF/dt* on the upper graph; O——O = *TPF* on the lower graph; * = $0.02 > p$; ** = $0.001 > p$ compared with the control value.

**TABLE**

**Changes in Isometric Force (F) and Maximum Velocity of Force Development (dF/dt) Associated with Administration of Protamine***

| | Concentrations of protamine ($10^{-3}$ g/L) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Heart muscle | Isometric force (*F*) (g/mm$^2$) | | | | *dF/dt* (g/sec$^1$/mm$^2$) | | | |
| | 0 | 12.5 | 25.0 | 50.0 | 0 | 12.5 | 25.0 | 50.0 |
| 1 | 6.24 | 6.15 | 6.02 | 5.63 | 35.8 | 35.8 | 36.2 | 32.2 |
| 2 | 5.78 | 5.69 | 5.41 | 5.02 | 32.9 | 33.8 | 31.3 | 28.2 |
| 3 | 6.24 | 6.24 | 6.12 | 5.48 | 34.8 | 33.3 | 32.2 | 29.2 |
| 4 | 6.30 | 6.15 | 6.00 | 5.32 | 31.4 | 31.0 | 30.0 | 25.5 |
| 5 | 5.76 | 5.76 | 5.64 | 4.88 | 29.1 | 29.4 | 28.1 | 23.8 |
| 6 | 4.81 | 4.86 | 4.75 | 4.42 | 29.3 | 28.6 | 27.8 | 25.9 |
| Mean | 5.86 | 5.81 | 5.66 | 5.13 | 32.2 | 32.0 | 30.9 | 27.5 |
| ± SE | 0.23 | 0.21 | 0.21 | 0.18 | 1.14 | 1.14 | 1.27 | 1.23 |
| *p* | | NS | $0.01 > p > 0.001$ | $0.001 > p$ | | NS | $0.05 > p > 0.02$ | $0.001 > p$ |

* All values were normalized by dividing the original values by the cross-sectional area of each muscle. p: level of statistical significance compared to control values.

Gourin et al[1] found that protamine causes a slight though not significant increase in left ventricular pressure and the rate of pressure raise using the total cardiopulmonary bypass technique in dog. On the other hand, Fadali et al[2] reported that protamine produces a significant decrease in *V*max in the intact canine heart. The isolated heart muscle preparation that we used, unlike the intact heart, is free from the influence of changes in pre- and after-load and alterations in the neurohumoral control mechanisms observed in the intact heart. It is, therefore, reasonable to state that a myocardial depression observed in this study is caused by a direct effect of protamine upon the myocardium. Moreover, this depression is caused by protamine itself, not by its preservative.

In the present study the decrease in *F* produced by protamine was accompanied by a decrease in *dF/dt* but with no change in the time to peak force (*TPF*). Sonnenblick[3] has suggested that *dF/dt* reflects the intensity of the active state and that *TPF* is proportional to the duration of the active state of muscle contraction. The results of the present study thus suggest that protamine produces a decrease in intensity but not in duration of the active state. The unaltered duration of the active state has been observed also during the administration of intravenous[4] but not inhalation anesthetics,[5,6] although both types of anesthetics decrease the intensity of the active state, i.e., *dF/dt*.

The doses of protamine most often used clinically range from 1–4 mg/kg of body weight. Assuming that the injected protamine distributes evenly into the circulating blood volume of 75 ml/kg of body weight, serum concentrations of protamine following the clinical administration would be $13.3 \times 10^{-3}$ to $53.3 \times 10^{-3}$ g/L. These are comparable to the concentrations used in the present study. Since only 4 mg/kg of protamine produces myocardial depression of only approximately 10%, the direct myocardial depressant action of protamine is only a minor factor in the etiology of the hypotension that may accompany the intravenous administration of protamine.

The modest myocardial depression produced by protamine, however, is easily counteracted by the administration of $CaCl_2$ or epinephrine.

## REFERENCES

1. Gourin A, Streisand RL, Stuckey JH: Total cardiopulmonary bypass, myocardial contractility, and the administration of protamine sulfate. J Thorac Cardiovasc Surg 61:160–166, 1971
2. Fadali MA, Papacostas CA, Duke JJ, et al: Cardiovascular depressant effect of protamine sulphate: experimental study and clinical implications. Thorax 31:320–323, 1976
3. Sonnenblick EH: Active state in heart muscle: its delayed onset and modification by inotropic agents. J Gen Physiol 50:661–676, 1967
4. Iwatsuki N: The effect of thiamylal and propanidid on the isolated heart muscle in comparison with CT 1341. Tohoku J Exp Med 110:34–40, 1973
5. Brown BR, Crout JR: A comparative study of the effects of five general anesthetics on myocardial contractility. 1. Isometric conditions. Anesthesiology 34:236–245, 1971
6. Iwatsuki N, Shimosato S: Diethyl ether and contractility of isolated cat heart muscle: comparison of inotropic effects of five anaesthetics at equipotent levels. Br J Anaesth 43:420–426, 1971

ANESTH ANALG
59:103-109, 1980

# Analysis of Ventilatory Depression by Enflurane during Clinical Anesthesia

W. M. Wahba, MB, BCh, MSc (McGill), FRCP(C)*

WAHBA, W. M.: Analysis of ventilatory depression by enflurane during clinical anesthesia. Anesth Analg 59:103–109, 1980.

Tracheal pressures during airway occlusion (an index of ventilatory drive), inspiratory time, alveolar ventilation, and $Pa_{CO_2}$ were measured in spontaneously breathing, healthy patients during enflurane:$N_2O$ anesthesia at various inspired concentrations of enflurane. The purpose was to describe more clearly the mechanism of intraoperative hypoventilation. Occlusion pressures, inspiratory time, and alveolar ventilation were less, and $Pa_{CO_2}$ was higher, at deeper levels of anesthesia. Hypoventilation is due to reduced mechanical transform of neuromuscular drive and to shorter inspiratory time and, therefore, reduced mean inspiratory flow rate without change in breathing frequency. Effective elastance (an index of lung stiffness) was slightly greater at deeper levels of anesthesia.

**Key Words:** VENTILATION: enflurane; ANESTHETICS, Volatile: enflurane.

THE EFFECTS of drugs on ventilation are usually examined by measuring minute ventilation ($\dot{V}E$) and arterial carbon dioxide tension at different concentrations of the drug, or by comparing the change in $\dot{V}E$ during $CO_2$ rebreathing before and after administration of the drug under consideration. Milic-Emili[1] suggested a method that makes the determination of $\dot{V}E$ more informative. By the simple, noninvasive method of timing the phases of ventilation (inspiratory and total time, $T_i$ and $T_{tot}$) and measuring the static pressure generated in the airway during occlusion of the latter (occlusion pressure $P^O$) at functional residual capacity (FRC), the ventilatory effects of drugs can be adequately described. Minute ventilation is the product of tidal volume ($V_T$) and frequency ($f$), i.e.

$$\dot{V}E = V_T \times f \qquad (1)$$

But since $V_T$ equals mean inspiratory flow rate ($V_T/T_i$) times duration of inspiration ($T_i$), and since $f$ equals the reciprocal of total cycle duration times 60 (i.e., $1/T_{tot} \times 60$), the classic equation can be rewritten as:

$$\dot{V}E = \frac{V_T}{T_i} \times \frac{T_i}{T_{tot}} \times 60 \qquad (2)$$

This form takes into account the mean inspiratory flow rate ($V_T/T_i$) as a result of driving pressure and the influence of duration of inspiration ($T_i/T_{tot}$).

The occlusion pressure as measured is an index of neuromuscular inspiratory drive and, as such, represents the potential energy available for tidal exchange.[2] It takes into account both central drive and muscle contraction, but cannot differentiate between them. For a given driving pressure, the resulting flow ($V_T/T_i$) depends on impedance to flow (Ohm's law). The ratio between some of the measurements can give valuable indices of pulmonary mechanics. By correlating timed occlusion pressures (e.g. at 0.1 or 0.5 seconds: $P^O$ 0.1 or $P^O$ 0.5) to the resultant flow, an index of lung mechanics at the time of measurement

---

* Assistant Professor, Department of Anaesthesia, McGill University.

Received from the Department of Anaesthesia, Queen Elizabeth Hospital of Montreal, 2100 Marlowe Ave, Montreal, Quebec, H4A 3L6, Canada. Accepted for publication October 1, 1979. Presented at the Annual Meeting of the American Society of Anesthesiologists, October 20-24, 1979, San Francisco, California.

is obtained. This can, alternatively, be obtained by examining the ratio of maximal occlusion pressure ($P^0$ max) and tidal volume.[3]

The approach described was taken to examine in greater detail the effects of different inspired enflurane concentrations in $N_2O$-$O_2$ on ventilation in lightly premedicated healthy adult patients during anesthesia for elective minor operations on the limbs. This anesthetic agent was chosen because there is scant information regarding its respiratory effects, particularly during clinical anesthesia.[4]

## Methods

The sample consisted of ten healthy adults (mean age: 32.5 ± 6 years) of normal body build (mean weight/height ratio: 0.4 ± 0.02) scheduled for elective operations on the limbs; they gave their consent to the study approved by the hospital Ethics and Research Committee. Because ventilation during enflurane anesthesia is significantly and directly related to the value of forced expiratory volume ($FEV_{1.0}$),[4] a prime condition for inclusion in the study was a preoperative $FEV_{1.0}$ of at least 85% of the value predicted for the patient's age and height. The mean $FEV_{1.0}$ actual/predicted for the patients studied was 96 ± 3%. All patients were given a mild tranquilizer (promethazine-HCl, 25 mg) intramuscularly as premedication 1 hour preoperatively. Anesthesia was induced intravenously by thiopental (3 to 5 mg/kg) followed by succinylcholine (1 mg/kg IV) to facilitate orotracheal intubation with a cuffed tube. Prior to intubation, the trachea and vocal cords were sprayed with 4% lidocaine (100 to 120 mg). Anesthesia was maintained with enflurane in $N_2O$ (4 L/min) and $O_2$ (3 L/min), using a non-rebreathing circuit with a low resistance unidirectional valve (Ambu-Hesse). In all instances, the patients were first given the higher inspired concentrations of enflurane and later the lower ones. The measurements were made at the end of a period of at least 20 minutes of exposure to each concentration. No measurements were made if there was evidence that the level of anesthesia was not appropriate for the surgery as suggested by changes in heart rate, blood pressure, pupillary size, or by movement or lacrimation. The number of measurements made was dictated solely by the duration of the operation, which ranged from 1-2 hours.

### Occlusion Pressures

The occluding device was a Magill bag mount with one end hermetically sealed, placed proximal to the non-rebreathing valve. Moving the lever in the appropriate direction allowed temporary interruption of airway gas flow during inspiration. The inspiratory line was occluded at the beginning of expiration such that the next breath, initiated at FRC, generated the occlusion pressure. In each case four to six readings were made, allowing eight to ten normal breaths between readings. The pressure generated in the endotracheal tube was measured by a Statham 23P pressure transducer calibrated with a water manometer. The pressure tracing was obtained by an appropriate recorder, connected to a Tektronix 412 monitor. The pressure tracings of the unoccluded breaths were used to determine $T_i$ and $T_{tot}$ (Fig 1).

### Minute Ventilation

A Wright respirometer placed between the endotracheal tube and the unidirectional valve was used to measure minute ventilation. Frequency was counted over 1 minute and tidal volume was calculated.

### Arterial $P_{CO_2}$

Arterial blood samples were taken from a peripheral artery by simple puncture. The blood was collected in heparinized syringes, which were then packed in ice. Arterial $P_{CO_2}$ was measured by standard electrodes in a Corning 165 blood gas analyzer. The electrodes were frequently calibrated with mixtures of 0, 5, and 10% $CO_2$. The analyses were performed

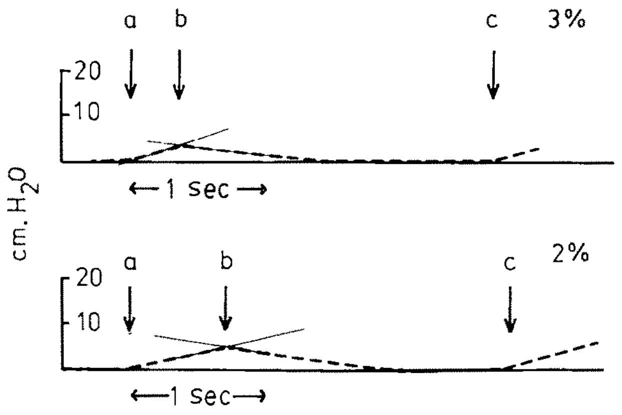


FIG 1. Determination of $T_i$ and $T_i/T_{tot}$ ratio. Pressure tracings during unoccluded breaths from the same subject at two different inspired enflurane concentrations are shown. Vertical axis is pressure (cm $H_2O$); horizontal axis is time (seconds). Inspiratory time ($T_i$) is duration between a clear-cut upswing and a net downswing of pressure tracing (points a to b). Total cycle duration ($T_{tot}$) is time between point a and onset of following upswing (point c). This was used to verify frequency as counted over a minute. The distinctly shorter $T_i$ at higher concentration is clearly seen.

within 10 minutes of sampling, introducing a possible error of less than 1 torr.[5]

The appropriate Student's t-test and regression analysis (by least squares method) were used in the statistical analysis of the results.

In one patient measurements of only occlusion pressures and $Pa_{CO_2}$ are reported because of technical difficulty with the respirometer connections.

## Results

### Ventilation and $Pa_{CO_2}$

In all instances $\dot{V}E$ was less at the higher inspired concentrations of enflurane. The Table gives the group data standardized for body size by the ratio of $\dot{V}E$ to surface area (in square meters). The concomitant higher $Pa_{CO_2}$ levels with deeper anesthesia are also reported in the Table. In a study such as this, it is vitally important that changes in the ventilatory wave form (spirogram) are taken into account, particularly to determine any changes in the direction of the convexity of the tracing. This is true because, for the same drive, a small change in $T_i$ reduces actual $V_T$ when the spirogram is concave upwards. This is not the case when the spirogram is convex upwards unless $T_i$ shortens considerably. We feel that the occlusion pressure tracing is an acceptable representation of the spirogram. There were no changes in the direction of the convexity of the $P^O$ tracing at the different concentrations of enflurane.

Respiratory frequency did not change (Table) and the changes in minute ventilation were, therefore, purely a function of changes in tidal volume. However, the duration of inspiration was markedly shortened at deeper levels, with a net lengthening of the expiratory phase (*Te*). There was a clear-cut trend to progressive lengthening of $T_i$ as anesthesia was lightened. This is shown in Fig 2 which plots the $T_i/T_{tot}$ ratio against inspired enflurane concentration. The influence of the relative duration of $T_i$ on $Pa_{CO_2}$ is given by the following relationship:

$$Pa_{CO_2} = 58.7 - 48.84\ T_i/T_{tot}\ (r = 0.47,\ p < 0.05)$$

The combined effect of these changes in tidal volume and in duration of inspiration was a reduction in mean inspiratory flow rate at deeper levels of anesthesia. Individual data are shown in Fig 3 and the group data are reported in the Table.

**TABLE**

**Measurements at Various Inspired Enflurane Concentrations (mean ± SE)**

| | Inspired enflurane concentration | | | |
|---|---|---|---|---|
| | 1.0% (n = 4) | 1.5% (n = 4) | 2.0% (n = 8) | 3.0% (n = 7) |
| Minute ventilation (L/min/m²) | 3.3<br>0.63 | 3.6<br>0.56 | 3.2<br>0.36 | 2.1*<br>0.24 |
| Frequency (breaths/min) | 20.5<br>2.0 | 24.0<br>3.2 | 22.9<br>1.6 | 20.9<br>1.6 |
| $Pa_{CO_2}$ (torr) | 38.0<br>3.0 | 40.0<br>4.0 | 47.2<br>5.0 | 51.2*<br>3.8 |
| Mean inspiratory flow rate ($V_T/T_i$) (L/sec) | 0.36<br>0.05 | 0.37<br>0.04 | 0.36<br>0.07 | 0.24*<br>0.04 |
| Impedance (cm $H_2O$ L/sec) | 17.9<br>4.0 | 25.0<br>7.0 | 24.0<br>5.0 | 27.2*<br>4.6 |

* Statistically significant ($p < 0.05$) from values at 1% or 1.5% enflurane.

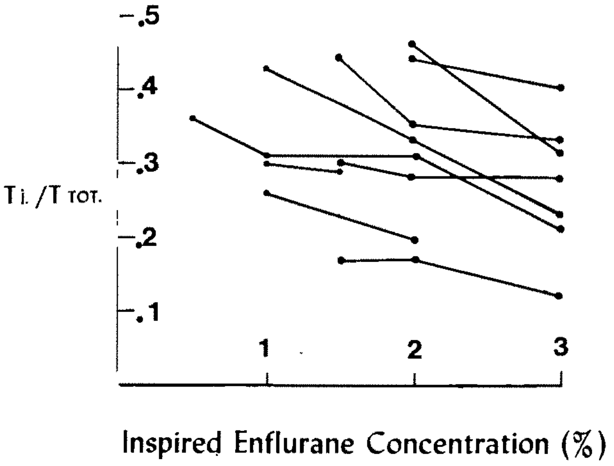


FIG 2. Relationship between depth of anesthesia and ratio of inspiratory time ($T_i$) to total respiratory cycle time ($T_{tot}$).

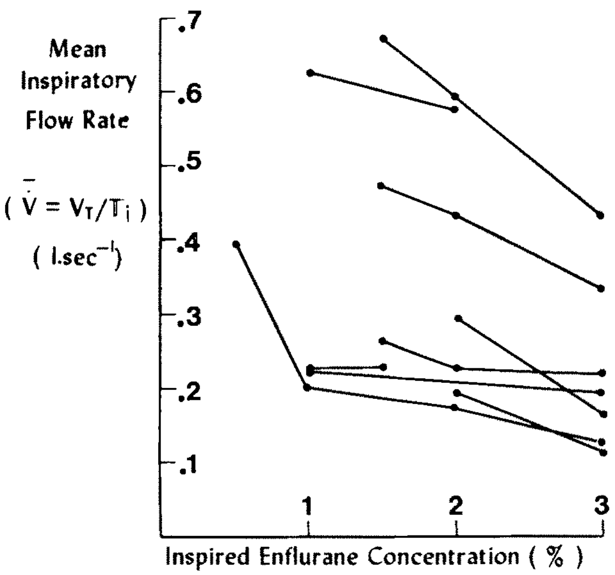


FIG 3. Mean inspiratory flow rate with depth of anesthesia. Mean inspiratory flow rate is ratio of tidal volume ($V_T$) to inspiratory time ($T_i$).

In the introduction, the standard equation $\dot{V}E$ =

$V_t \times f$ was changed to express $\dot{V}E$ as the product of two derivatives: mean inspiratory flow rate and the duty cycle ($V_T/T_i \times T_i/T_{tot}$). The contribution of both derivatives can be assessed by multiple linear regression. The general equation calculated was:

$$\dot{V}E/SA = 7.61\ V_T/T_i + 7.24\ T_i/T_{tot} - 1.65\ (r = 0.86,\ p \ll 0.001)$$

where SA is surface area in $m^2$. The coefficients of partial correlation were 0.75 for $V_T/T_i$ and 0.69 for $T_i/T_{tot}$.

### Occlusion Pressures

Occlusion pressure tracings from all the patients at each concentration of enflurane are shown in Fig 4. Patient identification numbers are underlined and the vaporizer setting is indicated as close to the pressure curve as possible. The vertical axis is pressure (in cm $H_2O$) and the horizontal axis is time (in seconds). Absolute values of maximal pressure ($P^O$ max) were less at deeper levels of anesthesia, as was the slope. The duration of the occluded breath (that is the horizontal distance from the first inflection to a net change in direction toward the baseline, $T_i^O$), varied from patient to patient without a clear-cut tendency to either lengthen or shorten. The area under a curve displaying tension exerted as a function of time is an expression of the mechanical work that the organ in question (in this instance, the diaphragm) can perform. In all instances the area (i.e., the time-tension index) was clearly less at deeper anesthetic levels.

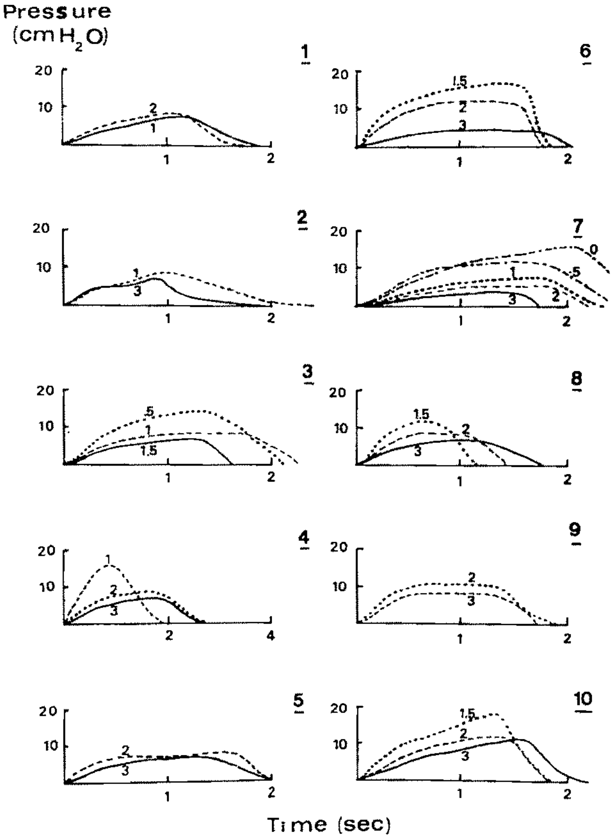


FIG 4. Airway occlusion pressures in all subjects. Vertical axis is pressure (cm $H_2O$); horizontal axis is time (seconds). Patient identification is larger underlined number; smaller number close to tracing is vaporizer setting. Paper speed was 50 mm/sec except in patient 4 (25 mm/sec).

These features indicate that ventilatory depression, in terms of $P^O$, manifests as reduced maximal pressure, reduced rate at which that pressure is attained, and a general reduction in the mechanical transform of that output.

### Pulmonary Mechanics

The ratio of pressure generated at a fixed time interval to $V_T/T_i$ indicates mechanical impedance to flow.[3] This ratio is usually expressed in terms of $P^O$ at 0.1 second. However, in the situation where the initial portion of the $P^O$ curve is, as in the present study, essentially linear throughout (i.e., the same initial slope), it is possible to use the value of $P^O$ at time intervals later than 0.1 second, for instance at 0.5 seconds. This reduces errors in measuring pressures. As anesthesia was lightened, individual values of $V_T/T_i$ and $P^O$ 0.5 increased. The increase was proportionate, however, and resulted in a nearly constant ratio between $P^O$ 0.5 and mean inspiratory flow rate (i.e., $V_T/T_i$). The individual data are shown in Fig 5.

The ratio between maximum occlusion pressure ($P^O$ max) and the tidal volume of the breath preceding occlusion has been called "effective" elastance of the respiratory system (E′rs).[3] The data in this study show a trend toward a slight increase in elastance at deeper levels of anesthesia. This trend is shown in Fig 6 together with mean data (± SEM). The coefficient of correlation is 0.4 ($p < 0.05$), indicating that increasing lung stiffness may be an important but not a major factor.

## Discussion

### Anesthetic Technique

The purpose of this study was to examine the ventilatory effects of enflurane during conventional clinical anesthesia and surgery. The protocol, therefore, precludes the interpretation of the results in terms of a pure pharmacologic study. However, every

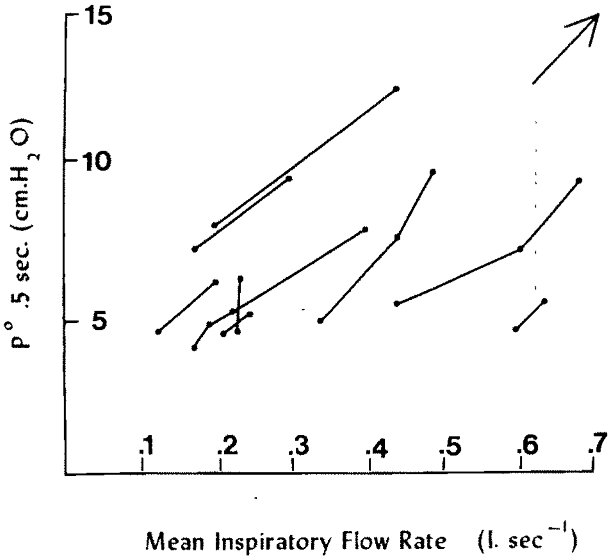


FIG 5. Relationship between P° at 0.5 sec and mean inspiratory flow rate. Arrow (upper right) indicates direction of lighter levels of anesthesia.

effort was made to minimize the effects of the other drugs given during the anesthetic. Narcotic premedication drugs were not used in order to avoid their ventilatory effects.[6] It is unlikely that either phenothiazine, with its antianalgesic effect, given 1 hour before induction, or the induction dose of thiopental, significantly influenced the measurements, the first of which were made 20 to 30 minutes after induction. It is not possible to evaluate the effects of $N_2O$.

A more major difficulty is the relationship between inspired and alveolar (i.e., central nervous system) enflurane concentrations. Without actually measuring alveolar or end-tidal enflurane concentration, it is impossible to state with certainty anesthetic depth. It seemed reasonable, however, that with a non-rebreathing technique, alveolar concentration would plateau in about 20 minutes in these healthy individuals, and that the dial setting of the vaporizer could serve as an acceptable approximation of alveolar concentration. We also attempted to minimize the result of changes in delivered concentrations by first examining the effects of higher concentrations and then making the measurements at progressively lower concentrations. In all instances, the measurements were made at the end of a period of at least 20 minutes in order to have an alveolar anesthetic concentration plateau at the time that the measurements were made. The possible effects of surgery on ventilation in the present study, whose purpose was to evaluate ventilation during clinical enflurane anesthesia and surgery, cannot be excluded.

A final point is the question of whether ventilatory adaptation may have occurred over a period of time.[7] No specific attempt to examine this point was made in the present study; it seems unlikely that adaptation accounts for the changes in ventilation noted because of the brief exposure.

## Results

The present study was undertaken to define more clearly the mechanisms of hypoventilation at various levels of enflurane anesthesia. Progressive hypoventilation with deepening anesthesia was found to be due to reduced mean inspiratory flow rates which were, in turn, due to reduced amplitude and slope of the occlusion pressure curve and to shortened inspiratory times. There was no change in breathing frequency in these unpremedicated subjects.

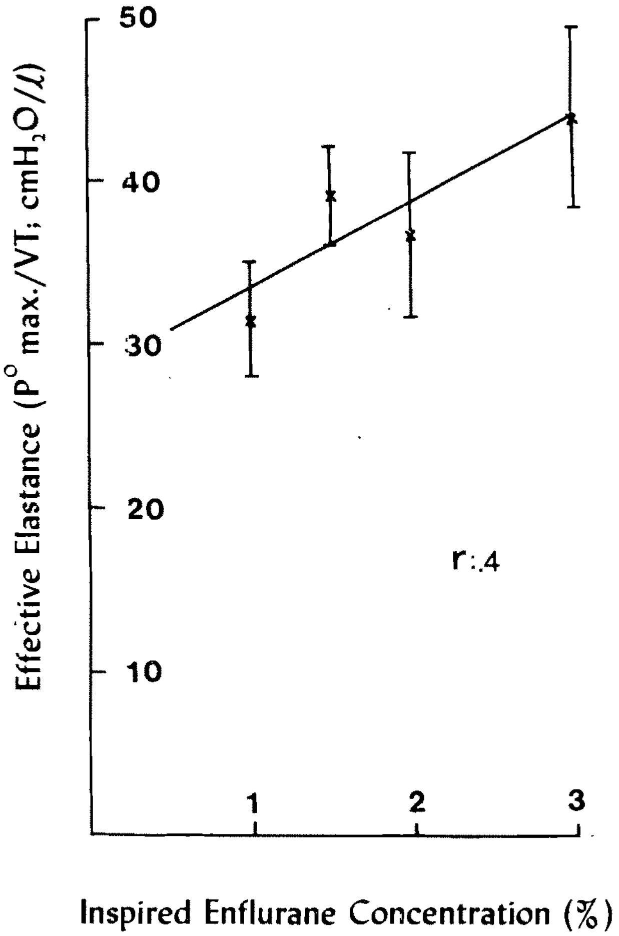


FIG 6. Effects of anesthetic depth on pulmonary elastance (mean data ± SEM). Elastance is ratio of maximal occlusion pressure (P° max) and tidal volume ($V_T$). Straight line describes relationship for all data derived by least squares linear regression. Intercept at 0% enflurane is 28 cm $H_2O$/L.

The observed changes in the value and slope of $P^O$ and, thus, the time-tension index indicate a clear-cut reduction in the mechanical transform of neuromuscular ventilatory drive. This reduction in mechanical efficiency may be either central, or peripheral, or both. Central neurogenic drive and chemoreceptor activity are probably depressed by enflurane in a manner similar to that of its isomer, isoflurane. In the context of the present study, depression of the central activity generator will certainly manifest as a reduced amplitude of $P^O$. However, the lack of change in rate of firing (frequency) and the significant reduction in slope of $P^O$ shown in Fig 4, particularly at deeper levels of anesthesia, suggest that the effector organs, the muscles of respiration, are significantly affected. This hypothesis rests upon two reported observations. The data reported by Sharp et al[8] are pertinent to this hypothesis. The intercostal muscles have a critical role when breathing in the supine position. The intercostals act as a strut to prevent rib cage deformation produced by the contracting diaphragm. Thus, for a given neural drive, the value of $P^O$ depends on the integrity of the rib cage muscles and diaphragm acting as a couple, and also upon the radius of curvature of the diaphragm. Enflurane has a dose-dependent, curare-like effect on muscles at an alveolar concentration of 2%.[9] Presumably the curarizing effects of enflurane qualitatively resemble those of curare itself, with diaphragmatic sparing until deeper anesthetic levels are attained. It is, therefore, only necessary to have a slight reduction in the strut effect of the rib cage muscles and a small increase in the radius of curvature of the diaphragm to obtain the low $P^O$ values with reduced slope at low alveolar enflurane concentration. This qualitatively resembles the effects of halothane anesthesia on rib cage musculature.[10,11] At deeper levels of anesthesia, the progressive paralyzing effects on the diaphragm itself will come into play, reducing amplitude and slope of $P^O$ further. Lebowitz et al[9] reported that the curare-like effects of enflurane cannot be reversed by neostigmine. The differentiation between central depression and peripheral effects on the muscles of respiration is, therefore, impossible. We are inclined to believe that the muscular effects play a predominant role. In terms of the efficiency of gas exchange, this mechanical inefficiency compounds the effects of the expected 60% increase in pulmonary elastance that immediately follows the induction of anesthesia.[12]

Although breathing frequency did not change, the duration of inspiration decreased at deeper levels of anesthesia and had a statistically significant inverse correlation with $Pa_{CO_2}$, indicating the importance of the duration of inspiration. The decrease in $T_i$ may represent central depression. But it is interesting to note that awake patients with chronic obstructive lung disease (COPD) and $CO_2$ retention have a much shorter $T_i$, compared with either patients with COPD without $CO_2$ retention or normal subjects (0.9 ± 0.2 seconds vs 1.5 ± 0.4 and 1.7 ± 0.3, respectively).[13] It seems, therefore, that shorter $T_i$s are common to patients breathing at a mechanical disadvantage and may be a homeostatic mechanism. Derenne, Macklem, and Roussos[14] have stated that the inspiratory on-and-off switching mechanism is influenced by, inter alia, reflexes arising from the lungs and the chest wall. One can envisage, therefore, that the smaller $T_i/T_{tot}$ ratio (also called the "duty cycle") is due to the peripheral effects of enflurane. This possibility fits with the hypothesis that central neurogenic drive in the present study may, in fact, have changed minimally with depth of anesthesia but that this minimal change was masked by the effect of enflurane on respiratory muscles, resulting in an inappropriate response to central neurogenic drive. By an entirely different line of reasoning, Derenne and colleagues proposed that the cause of hypoventilation during anesthesia with methoxyflurane (which does not have curare-like effects[15]), is peripheral rather than central in origin. The differences and similarities between the two studies must be examined closely in order to appreciate the reasoning that led to these suggestions. The conclusions of Derenne et al were based on the observation that the values of occlusion pressures measured during $CO_2$ rebreathing during methoxyflurane anesthesia at a constant concentration (0.3%) were almost identical with those that they had previously measured in awake subjects during $CO_2$ rebreathing. In the present study, occlusion pressures were less at deeper levels of anesthesia, an observation that may be largely due to respiratory muscle weakness. The study of Derenne et al, reported that mean effective elastance (when alveolar $P_{CO_2}$ was 55 torr) was 43.4 cm $H_2O$/L, a value much higher than that calculated for awake subjects. Their thesis was, therefore, that lung stiffness is primarily responsible for hypoventilation during methoxyflurane anesthesia manifesting as a ventilatory output that was inappropriate for the $CO_2$ stimulus. It has previously been reported[4] that ventilation during enflurane anesthesia is a direct function of $FEV_{1.0}$, a relationship that is probably due to the intraoperative reduction in pulmonary mechanical efficiency and in FRC, the extent of which is inversely related to $FEV_{1.0}$. It is interesting to note that mean effective elastance in the present study, when inspired enflurane concentration was 2 to 3%, was 39 to 44 cm $H_2O$/L. Furthermore, atropine increases pulmonary ventilation during enflurane anesthesia, presumably by reducing airway resistance.[16] It thus appears that hypoventilation during both enflurane and methoxyflurane anesthesia is due to the intraoperative mechanical properties of the ventilatory apparatus. The major difference between the two agents in question seems to be the dose-related curariform effect of enflurane on respiratory muscles which further decreases the efficiency of the ventilatory pump.

The hypothesis that hypoventilation during enflurane anesthesia is largely, or principally, peripheral (muscular) rather than central can be tested by examining the effects of different enflurane concentrations on rib cage vs diaphragmatic contributions to tidal breathing with electromyographic recording of the activity of the various muscles concerned as reported for halothane by Tusiewicz et al,[10] and Jones et al.[11]

The measurements made in the present study allow us to determine whether increasing lung stiffness plays a role in reducing ventilation during clinical enflurane anesthesia. Effective impedance to breathing is the ratio of timed occlusion pressure to mean inspiratory flow rate. In all the patients, both $P^{0}$ 0.5 and $V_T/T_i$ increased as anesthesia was lightened. The increase in both was proportional, resulting in a nearly constant value of the ratio (Fig 5 and Table). Another index of lung mechanics is effective elastance. In most subjects, there was a tendency for E'rs to be greater at deeper levels of anesthesia (Fig 6). The correlation between individual values and the inspired concentration was only 0.4 ( $p < 0.05$), however, indicating that increasing lung stiffness with anesthetic depth plays a relatively minor role in normal subjects breathing spontaneously during enflurane anesthesia.

In conclusion, progressive hypoventilation with increasing depth of enflurane anesthesia results from the less efficient mechanical transformation of neuromuscular ventilatory drive, together with a progressive shortening of the duration of inspiration. Increasing lung stiffness also plays a role. These effects compound the consequences of central depression by anesthesia and the increased impedance to gas flow usually found after induction of anesthesia.

## ACKNOWLEDGMENTS

Dr. D. M. M. Gillies provided valuable help throughout the investigation and preparation of this paper. Drs. A. C. Bryan and T. Trippenbach made useful suggestions during preparation of the text. Ohio Chemical Products, Canada, donated financial support for the purchase of a desk-top calculator for the statistical analysis.

## REFERENCES

1. Milic-Emili J: Recent advances in the evaluation of respiratory drive. Int Anesthesiol Clin 15:39-58, 1977
2. Eldridge FL: Relationship between respiratory nerve and muscle activity and muscle force output. J Appl Physiol 39:567-574, 1975
3. Derenne JP, Couture J, Iscoe S, et al: Occlusion pressures in men rebreathing $CO_2$ under methoxyflurane anesthesia. J Appl Physiol 40:805-814, 1976
4. Wahba WM: Influence of airway resistance and ventilatory pattern on $PaCO_2$ during enflurane anaesthesia. Br J Anaesth 51:123-126, 1979
5. Kelman GR, Nunn JF: Nomograms for correction of blood, $PO_2$, $PCO_2$, pH and base excess for time and temperature. J Appl Physiol 21:1484-1490, 1966
6. Knill R, Cosgrove JF, Olley PM, et al: Components of respiratory depression after narcotic premedication in adolescents. Can Anaesth Soc J 23:449-458, 1976
7. Calverley RK, Smith NT, Jones CW, et al: Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. Anesth Analg 57:610-618, 1978
8. Sharp TJ, Goldbert NB, Drutz WS, et al: Relative contribution of rib cage and abdomen to breathing in normal subjects. J Appl Physiol 39:608-618, 1975
9. Lebowitz MH, Blitt CD, Walts LF: Depression of twitch response to stimulation of the ulnar nerve during ethrane anesthesia in man. Anesthesiology 33:52-57, 1970
10. Tusiewicz K, Bryan AC, Froese AB: Contributions of changing rib-cage diaphragm interactions on the ventilatory depression of halothane anesthesia. Anesthesiology 47:327-337, 1977
11. Jones JG, Faithful D, Jordan C, et al: Rib cage movement during halothane anaesthesia in man. Br J Anaesth 51:399-407, 1979
12. Derenne JP, Couture J, Whitelaw WA, et al: Interaction between the mechanical properties of the respiratory system and drive in the control of breathing of anesthetized man, in Regulation of Respiration in Sleep and Anesthesia. Edited by R S Fitzgerald, M Gautier, S Lahiri. New York, Plenum Press, 1978, pp 105-116
13. Sorli J, Grassino A, Lorange G, et al: Control of breathing in patients with chronic obstructive lung disease. Clin Sci Mol Med 54:1-10, 1978
14. Derenne JP, Macklem PT, Roussos CL. The respiratory muscles: mechanics, control and pathophysiology (part II). Am Rev Respir Dis 118:373-390, 1978
15. Ngai SH, Hanks EC: Effects of methoxyflurane on electromyogram, neuromuscular transmission and spinal reflex. Anesthesiology 23:158, 1962
16. Wahba WM, Sadkova J: Atropine reversal of hypercarbia during enflurane anaesthesia. Br J Anaesth 51:221-226, 1979

ANESTH ANALG
59:110-116, 1980

# Clinical Characteristics of Long-Term Succinylcholine Neuromuscular Blockade during Balanced Anesthesia

**Frederic M. Ramsey, MD,* Philip W. Lebowitz, MD,* John J. Savarese, MD,† and Hassan H. Ali, MD‡**

---

RAMSEY, F. M., LEBOWITZ, P. W., SAVARESE, J. J., AND ALI, H. H.: Clinical characteristics of long-term succinylcholine neuromuscular blockade during balanced anesthesia. Anesth Analg 59:110–116, 1980.

Thumb adductor twitch response to train-of-four (2 Hz for 2 seconds) stimulation of the ulnar nerve was used to assess the clinical characteristics of long-term neuromuscular blockade induced with continuous infusion of succinylcholine during balanced ($N_2O$-$O_2$-narcotic-thiopental) anesthesia. Twitch depression of 80 to 90% was maintained for 86 to 365 minutes by continuous infusion of succinylcholine at 86 ± 5(SEM) $\mu$g/kg/min. Of 32 patients, 24 developed phase II block, defined as a train-of-four ratio of less than 50%. There was a large degree of individual variability in sensitivity to development of phase II block. This precluded defining a narrow dose range where transition from phase I to phase II occurred. Tachyphylaxis occurred in 25% of patients and was independent of the type of block. Neither dose nor duration of infusion was predictive of spontaneous recovery rate from phase II block. Of 24 patients who developed phase II block, 50% recovered spontaneously at a rate comparable to the recovery rate from a phase I block. The other 50% manifested prolonged recovery of neuromuscular function. After observing spontaneous recovery in these patients for 31 ± 5(SEM) minutes, successful antagonism of residual phase II block with anticholinesterase agents was achieved.

**Key Words:** NEUROMUSCULAR RELAXANTS: succinylcholine; MEASUREMENT TECHNIQUES: neuromuscular blockade.

---

AS DOSE and duration of succinylcholine (SCh) administration increase, the characteristics of the induced neuromuscular block change from depolarizing to non-depolarizing or phase II block. Classically this is manifested by fade to tetanic stimulation, post-tetanic facilitation, and antagonism of the block by anticholinesterase (anti-ChE) agents.[1-6] The development of phase II block may coincide with delayed recovery of neuromuscular transmission.[5-8] Using train-of-four fade as an indicator of transition, Lee[8] found a slow recovery of thumb twitch associated with transition from phase I to phase II block in patients during inhalation anesthesia with halothane. Savarese et al[9] demonstrated the clinical usefulness of train-of-four monitoring in the management of prolonged neuromuscular blockade following SCh in patients with atypical plasma cholinesterase.

With train-of-four nerve stimulation, a depolariz-

---

* Instructor in Anaesthesia.

† Associate Professor of Anaesthesia.

‡ Assistant Professor of Anesthesia.

Received from the Anesthesia Services of the Massachusetts General Hospital and the Department of Anesthesia, Harvard Medical School, Boston, Massachusetts 02114. Accepted for publication October 15, 1979.

Reprint requests to Dr. Ramsey, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

ing block results in equal inhibition of all four twitches in the train, while the development of phase II block from SCh is evidenced by marked diminution in the height of the fourth twitch relative to that of the first, i.e., "fade." Train-of-four monitoring provides reliable assessment of neuromuscular transmission without altering the response to successive stimuli. This is in contrast to tetanic stimulation, which augments post-tetanic twitch height and has a "decurarizing effect."[10] The train-of-four technique allows the quantification of fade to be tested as frequently as every 10 seconds, thus improving the accuracy of determining changes in the characteristics of a SCh-induced block.

Utilizing the train-of-four stimulus pattern, we studied the clinical characteristics of long-term SCh neuromuscular blockade during balanced anesthesia for surgical procedures lasting up to 6 hours. The study was performed to determine the incidence of phase II block during prolonged administration of SCh. We measured the dose and duration of SCh administration required to produce phase II block, and the duration required for spontaneous recovery from the block. The recovery rate of patients who developed phase II block was compared with similar data obtained in patients who maintained phase I block. In patients demonstrating prolonged recovery from phase II block, we determined the effect of anti-ChE agents on the recovery pattern.

## Methods

Thirty-two consenting surgical patients, ranging in age from 20 to 71 years with an A.S.A. clinical status of I or II, were studied. No patient had clinical evidence of neuromuscular disease; none was taking drugs known to affect neuromuscular transmission.

Anesthesia was induced with a sleep dose of thiopental (3 to 5 mg/kg) and maintained with $N_2O$ and $O_2$ at 4 and 2 L/min, respectively, administered via a semiclosed circle system with $CO_2$ absorber. Narcotics (morphine, 0.2 mg/kg, or meperidine, 1.5 mg/kg) and additional thiopental were administered intravenously in accordance with anesthetic requirements. Ventilation was controlled with an Ohio volume-cycled ventilator adjusted to deliver 10 to 12 cc/kg at a rate of 8 breaths/minute. Muscle relaxation was achieved with a bolus of SCh (1 mg/kg IV) to facilitate tracheal intubation and maintained by continuous infusion of SCh (0.4%) via an IMED (model 922) volumetric infusion pump.

Cardiovascular monitoring included blood pressure by sphygmomanometer, heart rate by esophageal stethoscope, and oscillographic display of lead II of the electrocardiogram except when more invasive monitoring was deemed necessary because of the nature of the surgical procedure.

Square wave pulses 0.2 msec in duration at 2 Hz for 2 seconds (train-of-four stimuli) were delivered at supramaximal voltage by a Grass S88 stimulator through an isolation unit (model SIU5) to the ulnar nerve via 23-gauge steel needle electrodes placed subcutaneously over the ulnar nerve at the wrist. Successive train-of-four stimuli were delivered at a frequency of 0.1 Hz. The adductor twitch response of the thumb was recorded on a Grass (model 7C) polygraph via a Grass (FT-10) force transducer.

When twitch began to recover after the 1-mg/kg intubating dose of SCh, the continuous infusion of SCh (0.4%) was begun. The infusion rate was adjusted to maintain the height of the first twitch ($T_1$) in each train-of-four at 10 to 20% of control twitch height ($T_c$). The steady-state infusion rate required to maintain 80 to 90% twitch depression was determined and expressed in micrograms per kilogram per minute. Tachyphylaxis was considered to occur if greater than a 20% increase in rate of SCh infusion became necessary to maintain 80 to 90% twitch depression. The criterion for development of phase II block was chosen as the point where the fourth twitch ($T_4$) in a train-of-four response became less than 50% of the height of the first twitch ($T_1$) in the same train ($T_4/T_1 < 50\%$).

When surgical relaxation was no longer required, the SCh infusion was discontinued, and spontaneous recovery of the train-of-four response was observed. The time from 25% to 95% recovery of single twitch was measured in patients who recovered to 95% of control. Patients whose first twitch failed to reach 95% of control or whose train-of-four ratio was less than 60% at conclusion of surgery were given edrophonium, 0.1 mg/kg, and atropine, 0.4 mg, approximately 30 minutes following the conclusion of SCh infusion as a trial of antagonism of residual phase II block. If edrophonium produced a distinct improvement in twitch height, then neostigmine (1.0 to 2.5 mg) and atropine (0.4–1.0 mg) were also given 5 to 10 minutes later. The effects of anti-ChE agents on twitch and train-of-four responses were recorded. Nitrous oxide was then discontinued; extubation was performed after the patient demonstrated ability to sustain head lift for 5 seconds.

All doses of SCh include the 1-mg/kg bolus to facilitate tracheal intubation. Duration of administration extends from the time of the 1-mg/kg bolus until the infusion was stopped. All values in the text are means ± standard errors of the mean (SEM). Means, standard errors of the mean, and ranges are included in the tables. Statistical significance between groups was tested using an analysis of variance. Differences were considered statistically significant when $p < 0.05$.

## Results

Table 1 summarizes the data for all 32 patients included in the study. The total SCh dose was 13.0 ± 1.0 mg/kg and the duration of administration was 168 ± 13 minutes. The shortest duration of infusion was 86 minutes with a total dose of 5.0 mg/kg, and the longest period of administration was 365 minutes with a total dose of 21.0 mg/kg. Five patients received more than 20 mg/kg, the greatest dose being 29.3 mg/kg. The steady-state infusion rate required to maintain 80 to 90% twitch depression was 86 ± 5 μg/kg/min.

The 32 patients are divided into two groups, depending on whether or not they met the criteria for development of phase II block. Eight (group I) of 32 patients never developed phase II block, i.e., the $T_4/T_1$ ratio always exceeded 50%. These patients received 9.2 ± 1.4 mg/kg of SCh over a period of 111 ± 9 minutes. The steady-state infusion rate required to maintain 80 to 90% twitch depression was 78 ± 6 μg/kg/min. Twenty-four (group II) of the 32 patients developed a phase II block, defined by $T_4/T_1$ less than 50%. These patients received 14.3 ± 1.2 mg/kg of SCh over a span of 187 ± 15 minutes. The steady-state infusion rate required to maintain 80 to 90% twitch depression in group II was 88 ± 7 μg/kg/min. The mean total dose and mean total duration of SCh administration were significantly greater ($p < 0.05$) in group II than group I. Although the steady-state infusion rate was slightly greater in group II than group I, the difference was not statistically significant.

**TABLE 1**

**High-Dose Succinylcholine Administration during Balanced Anesthesia***

| Group | N | Dose | Duration of SCh administration | Steady-state infusion rate |
|---|---|---|---|---|
| | | *mg/kg* | *min* | *μg/kg/min* |
| I + II (total) | 32 | 13.0 ± 1.0<br>5.0–29.3 | 168 ± 13<br>86–365 | 86 ± 5<br>32–175 |
| I (phase I) | 8 | 9.2 ± 1.4†<br>5.0–17.2 | 111 ± 9†<br>86–155 | 78 ± 6<br>60–110 |
| II (phase II) | 24 | 14.3 ± 1.2†<br>5.9–29.3 | 187 ± 15†<br>87–365 | 88 ± 7<br>32–175 |

* Values are means ± SEM and range.

† Group I dose and duration significantly less than group II, $p < 0.05$.

The data from group II are presented in further detail in Table 2. The 24 patients are divided into two subgroups, depending on whether recovery from phase II block was entirely spontaneous (group IIA), or enhanced by anti-ChE agents (group IIB). The 12 patients in group IIA who recovered spontaneously received 12.8 ± 1.4 mg/kg of SCh over 162 ± 21 minutes. The 12 patients in group IIB received 15.9 ± 1.9 mg/kg of SCh over 211 ± 20 minutes. Although group IIB received more SCh over a longer period than did group IIA, the difference was not statistically significant. Similarly, the steady-state infusion rates required to maintain 80 to 90% twitch depression did not differ significantly between the two groups.

The onset of phase II block (the dose and time at which $T_4/T_1$ reached 50%) occurred after 6.8 ± 1.3 mg/kg of SCh at 98 ± 20 minutes in group IIA and after 6.7 ± 1.2 mg/kg of SCh at 88 ± 10 minutes in group IIB. The difference was not statistically signif-

**TABLE 2**

**Development of Phase II Block during Succinylcholine Infusion***

| Group | N | Entire dose | Entire duration | Onset of Phase II: Dose | Onset of Phase II: Duration of SCh administration | Steady-state infusion rate |
|---|---|---|---|---|---|---|
| | | *mg/kg* | *min* | *mg/kg* | *min* | *μg/kg/min* |
| II | 24 | 14.3 ± 1.2<br>5.9–29.3 | 187 ± 15<br>87–365 | 6.8 ± 0.9<br>2.3–17.9 | 93 ± 11<br>42–280 | 88 ± 7<br>32–175 |
| IIA (spontaneous recovery adequate) | 12 | 12.8 ± 1.4<br>5.9–21.7 | 162 ± 21<br>87–365 | 6.8 ± 1.3<br>2.5–17.9 | 98 ± 20<br>44–280 | 98 ± 12<br>60–175 |
| IIB (spontaneous recovery inadequate) | 12 | 15.9 ± 1.9<br>10.0–29.3 | 211 ± 20<br>103–355 | 6.7 ± 1.2<br>2.3–16.5 | 88 ± 10<br>42–159 | 78 ± 7<br>32–125 |

* Values are means ± SEM and range.

icant. The earliest onset of phase II block occurred at 2.3 mg/kg of SCh after 42 minutes of administration. In contrast, one subject failed to develop phase II block until 17.9 mg/kg of SCh had been given over 280 minutes. Fig 1 illustrates the development of phase II block in a patient as a function of dose and time.

Twelve (group IIA) of the 24 patients who developed phase II block recovered spontaneously to 95.5 ± 0.4% of control twitch within 15 ± 3 minutes without pharmacologic antagonism. The 25 to 95% twitch recovery time in these patients was 12.7 ± 2.4 minutes. The comparable recovery time for the patients in group I who never developed phase II block was 9.9 ± 2.6 minutes. Although the patients in group IIA recovered at a slower rate than those in group I, the mean difference was only 2.8 minutes and was not statistically significant. Fig 2 demonstrates spontaneous recovery from phase II block in two patients; one recovered in less than 10 minutes (Fig 2, top) and one required 28 minutes (Fig 2, bottom) for adequate recovery.

Additional data on recovery from phase II block are presented in Table 3. The 12 patients in group IIA who recovered rapidly from phase II block achieved 99.5% single twitch recovery, and the train-of-four value recovered to 83% within 15 ± 3 minutes. Eleven of the 12 patients in group IIB who demonstrated inadequate spontaneous recovery received anti-ChE agents as a trial of antagonism of residual phase II block. One patient in group IIB was electively ventilated postoperatively so antagonism was not attempted.

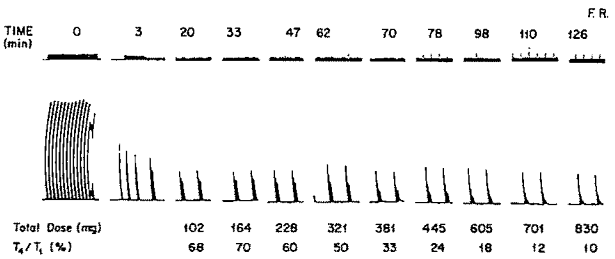
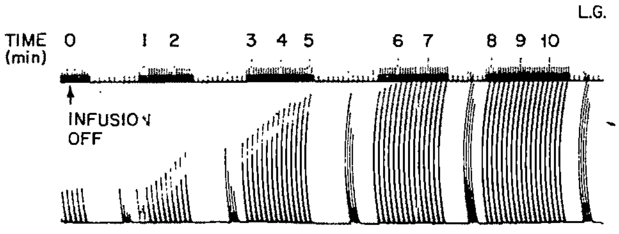
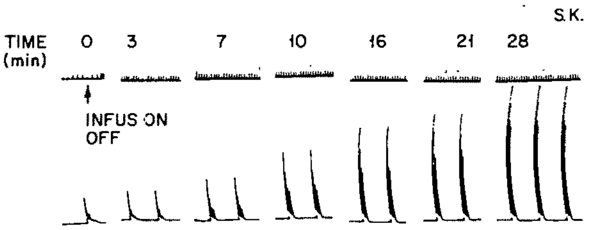


FIG 1. Development of phase II block during continuous succinylcholine infusion. At 62 minutes after 321 mg of SCh, $T_4/T_1$ was 50% (onset phase II). With continued administration of SCh the degree of fade progressed so that at 126 minutes after 830 mg of SCh $T_4/T_1$ was 10%.



Total Dose-594 mg (8.9 mg/kg); Duration-108 min



Total Dose-1084 mg (15.5 mg/kg); Duration-207 min

FIG 2. Top, rapid spontaneous recovery from phase II block following continuous succinylcholine infusion in a patient who received 8.9 mg/kg of SCh over 108 minutes. When the infusion was stopped, $T_1$ was 20% of $T_c$ and the train-of-four value was 25%. Ten minutes after SCh was stopped, $T_1$ was 100% of $T_c$ and $T_4/T_1$ was 85%. Bottom, more prolonged spontaneous recovery from phase II block following continuous succinylcholine infusion in a patient who received 15.5 mg/kg of SCh over 207 minutes. Twenty-eight minutes after SCh was stopped, $T_1$ was 100% of $T_c$ and $T_4/T_1$ was 70%.

Prior to attempted antagonism with endrophonium, spontaneous recovery of the train-of-four response was observed for a period of 31 ± 5 minutes. During

**TABLE 3**

**Recovery from Succinylcholine-Induced Phase II Block***

| Group | N | Recovery mode | Degree of spontaneous recovery | | Time to maximum spontaneous recovery | Recovery after antagonism | |
|---|---|---|---|---|---|---|---|
| | | | $T_1/T_c$ | $T_4/T_1$ | | $T_1/T_c$ | $T_4/T_1$ |
| | | | % | | *min* | % | |
| IIA | 12 | Spontaneous | 99.5 ± 0.4<br>95–100 | 83 ± 3<br>65–94 | 15 ± 3<br>5–33 | NA†<br>NA | NA<br>NA |
| IIB | 11 | Antagonized | 76 ± 5<br>53–100 | 48 ± 6<br>16–69 | 31 ± 5<br>21–65 | 99.5 ± 0.5<br>95–100 | 81 ± 3<br>62–100 |
| IIB | 1 | Spontaneous (left intubated electively) | 67 | 43 | 28 | NA | NA |

* Values are means ± SEM and ranges except for one patient in group IIB.

† NA, not applicable.

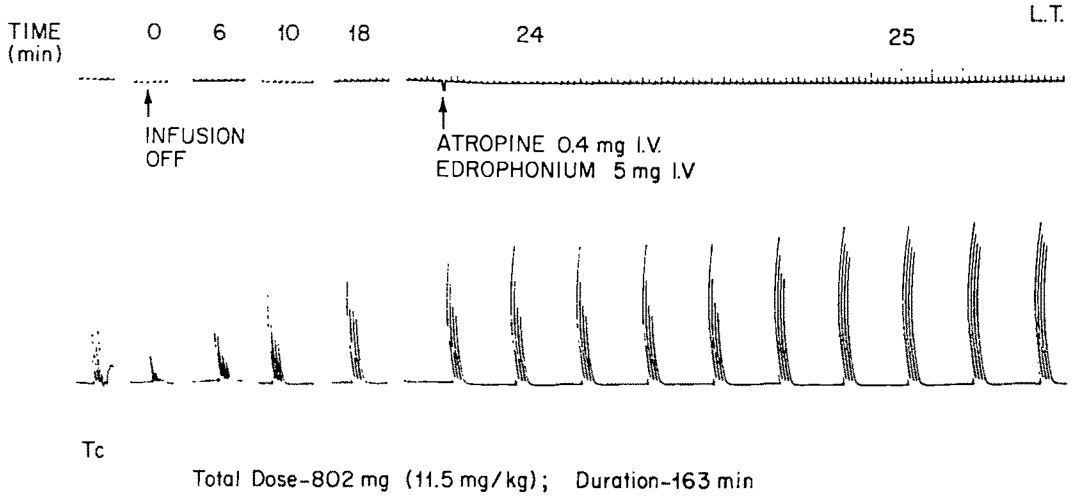


FIG 3. Edrophonium antagonism of phase II block produced by continuous succinylcholine infusion. Patient had received 11.5 mg/kg of SCh over 163 minutes. During 23 minutes of spontaneous recovery, twitch recovered to 80% of control and the train-of-four value reached 43%. Administration of edrophonium (5 mg) with atropine (0.4 mg IV) resulted in prompt recovery of $T_1$ to 95% of $T_c$ and $T_4/T_1$ to 86%.

this period $T_1$ recovered to 76% of $T_c$ and $T_4/T_1$ improved to 48%. Following edrophonium (0.1 mg/kg) and neostigmine (0.015 mg/kg), $T_1$ promptly improved to 99.5% of $T_c$ and $T_4/T_1$ increased to 81%. The block did not worsen in any patient following administration of anti-ChE agents. Fig 3 demonstrates pharmacologic antagonism of residual phase II block from SCh.

Tachyphylaxis to SCh, manifested by a 20% or greater increase in rate of infusion to maintain 80 to 90% twitch depression, was noted in eight of the 32 patients. Two of these subjects (group I) never developed phase II block. Of the six demonstrating tachyphylaxis who developed phase II block, four recovered spontaneously (group IIA), and two received anti-ChE agents (group IIB) to antagonize residual phase II block.

One patient in group IIB required 32 μg/kg/min of SCh to maintain 80 to 90% twitch depression, substantially less than the other patients in the study needed. This patient's dibucaine number was 73; however, plasma esterase activity was 66 μM acetylcholine/hour/ml (normal range 150 to 300). In this patient after 28 minutes of spontaneous recovery $T_1$ was 75% of $T_c$ and $T_4/T_1$ was 33%. After edrophonium (10 mg) and neostigmine (2.5 mg), $T_1$ recovered to 100% of $T_c$ and $T_4/T_1$ improved to 82%.

## Discussion

In our study, 75% of patients undergoing balanced anesthesia who received continuous SCh infusion to achieve 80 to 90% twitch depression for 86 to 365 minutes developed phase II block. We found great individual variability in both the dose of SCh and duration of infusion necessary to produce phase II block. This is consistent with earlier reports of Katz et al,[3] Katz and Ryan,[5] Crul et al,[6] and Sokoll and Bastron.[7] Although the patients who developed phase II block received significantly more SCh over a longer period than did patients who maintained phase I block, the variability was so great that we cannot define a dose of SCh or duration of administration for which one can expect the transition to occur. We suspect that the eight patients in group I would have progressed to phase II block had they received sufficient amounts of SCh. The fact that the total dose and duration of SCh infusion in this group was greater than that necessary to produce phase II block in group II indicates that the group I patients were, on the average, more resistant to developing phase II block than those included in group II. One patient in group II, who received 29 mg/kg of SCh, did not manifest 50% fade of the train-of-four response until 16 mg/kg had been administered. This patient would have been in group I had the dose of SCh been less than 16 mg/kg, i.e., if the procedure had been shorter. Because individual variability is so great, one cannot predict in advance what dose of SCh is sufficient to produce phase II block. In general, the likelihood increases with continued administration of the drug.

With continuous administration of SCh, we found the response to train-of-four stimulation to progress gradually from minimal fade, characteristic of a depolarizing block, to a marked degree of fade, consistent with a non-depolarizing or phase II block. Although we have arbitrarily defined a significant phase II block as one in which the train-of-four fade is 50% or greater, this does not imply an abrupt onset of phase II, as reported by Lee.[11, 12] During both halothane and enflurane anesthesia, Lee found a narrow dose range (3–5 mg/kg) where train-of-four rapidly faded concurrent with the onset of tachphylaxis. The membrane-stabilizing effects of potent inhalation agents used in Lee's studies may have magnified the phase II effect and caused it to become manifest at lower doses than we found during balanced anesthesia.

With continuous infusion of SCh during enflurane anesthesia, Lee and co-workers[13] observed a short-lasting steady state of neuromuscular blockade followed by a longer lasting steady state which coincided with phase I and phase II blocks, respectively. They found the onset of tachyphylaxis to be associated with transition from one steady state (phase I) to the other (phase II). Since depolarizing and non-depolarizing blocks are antagonistic, they concluded that tachyphylaxis resulted at least in part from "self-antagonism" between the depolarizing (phase I) and non-depolarizing (phase II) effects of SCh.

Contrary to Lee's results, during balanced anesthesia we did not find tachyphylaxis to be associated with transition from phase I to phase II block. Tachyphylaxis occurred in eight of the 32 patients, but occurred with equal frequency (25%) in the phase I and phase II groups. Our results do not support the theory of self-antagonism between phase I and phase II as an explanation for tachyphylaxis. Possible alternative explanations for tachyphylaxis include enzyme induction leading to increased metabolism of SCh and decreased plasma levels for a given rate of infusion or a change in receptor sensitivity to SCh with time. Since we are unaware of any evidence for induction of plasma cholinesterase we suspect that tachyphylaxis represents a change in end-organ sensitivity to SCh. Our results indicate that tachyphylaxis can occur whether the block is depolarizing or phase II in character. Therefore, during balanced anesthesia, development of tachyphylaxis cannot be relied upon to indicate a change in the nature of the block from phase I to phase II. Also, since the steady-state infusion rate required to maintain 80 to 90% twitch depression did not differ between the phase I and phase II groups, it cannot be used as an indicator or predictor of phase II block either.

Katz and Ryan[5] found that four of nine patients who received a continuous infusion of SCh for 2 hours required 51 to 69 minutes for single-twitch recovery. In a study by Crul and co-workers,[6] 20 of 28 patients developed phase II block during administration of SCh. Full recovery of twitch and tetanus was more prolonged in patients with phase II block than in patients who maintained a phase I block. Lee et al[11] found an abrupt onset of slow recovery in train-of-four response associated with marked train-of-four fade which occurred over a narrow dose range.

Our results are at variance with Lee's findings, possibly because of the different anesthetic techniques employed. Of the 24 patients in our study who developed phase II block, 12 (group IIA) spontaneously recovered adequate neuromuscular function within 12.7 ± 2.4 minutes. Although this was a slightly slower rate of recovery than that of the patients in group I who maintained phase I block, the difference was not significant. The other 12 patients (group IIB) did not recover adequate neuromuscular function within 31 ± 5 minutes, as indicated by $T_1$ less than 95% of $T_c$ and $T_4/T_1$ less than 60%. These patients received edrophonium and neostigmine to antagonize residual phase II block. Although the patients who received anti-ChE agents (group IIB) to antagonize a residual block received slightly more SCh (15.9 vs 12.8 mg/kg) over a longer period (211 vs 162 minutes) than those who recovered spontaneously (group IIA), the differences were not statistically significant. Thus, among patients developing phase II block, neither dose nor duration of SCh administration served as reliable predictors of spontaneous recovery rate or suggested the need for eventual antagonism of residual phase II block.

Churchill-Davidson and associates[2] demonstrated the ability of anti-ChE agents to antagonize phase II block from SCh. Katz et al[3] found that edrophonium antagonized the block produced by SCh in all patients who received more than 3 mg/kg. Nevertheless, Gissen and co-workers[14] asserted that the use of long-acting anticholinesterases was contraindicated at any time during or after the use of depolarizing compounds. They reasoned that should any circulating SCh be present, administration of an anti-ChE agent would inhibit hydrolysis of SCh and lead to enhancement rather than antagonism of the block. They also stated that recovery should be prompt even after prolonged administration of SCh, provided that the rate of administration did not exceed that required for complete blockade.

Sokoll and Bastron[7] successfully reversed phase II block with edrophonium in patients who manifested residual phase II block 30 minutes after SCh was discontinued. Lee[8] found that a train-of-four ratio of less than 0.4, measured when twitch was 30 to 50% of control, was associated with effective antagonism of phase II block by edrophonium. The greater the fade in train-of-four, the more effective the antagonism became. On the other hand, when the train-of-four ratio was greater than 0.4, Lee found that edrophonium enhanced the block.

Spontaneous but incomplete recovery in group IIB was observed for 31 ± 5 minutes prior to edrophonium administration. Neuromuscular function in these patients had partially recovered from 90% inhibition of twitch. Recovery of twitch had reached a plateau at 76 ± 5% of $T_c$ with further increase in twitch height progressing at only 0.4% of $T_c$ per minute before anti-ChE agents were given. No anti-ChE agent was given less than 20 minutes after stopping the SCh infusion so circulating levels of SCh should have been negligible. Under these conditions we found that residual phase II block following SCh administered by continuous infusion for up to 6 hours in doses exceeding 20 mg/kg could be antagonized with anticholinesterase agents. The concern that anti-ChE drugs, which also inhibit plasma cholinesterase, might prolong the block by preventing SCh hydrolysis, was inconsequential under the conditions of our study.

Our study shows that the development of phase II block with continuous SCh administration during balanced anesthesia is a gradual process. The degree of fade to train-of-four stimulation progresses with continued administration of the drug. A great degree of individual variability exists with regard to the dose of SCh sufficient to produce phase II block. Thus, a narrow dose range where one can expect phase II block to develop cannot be defined. Neither the rate of SCh administration required for 80 to 90% twitch depression nor the occurrence of tachyphylaxis was a reliable predictor of the onset of phase II block. The rate of spontaneous recovery from phase II block in our patients was extremely variable. Although some patients recovered rapidly, whether the block was depolarizing or phase II in character, approximately 50% of those developing phase II block experienced a prolonged recovery lasting ½ hour or more. We suggest that antagonism of a SCh-induced phase II block with anti-ChE agents may be attempted after spontaneous recovery of twitch has been observed for a period of 20 to 30 minutes and has reached a plateau phase with further recovery proceeding slowly. In this situation edrophonium and neostigmine invariably produce dramatic acceleration of the return of train-of-four toward normal. We strongly recommend that monitoring of neuromuscular function be performed when using SCh by continuous infusion for surgical relaxation. Train-of-four monitoring is useful in avoiding SCh overdose, detecting the development of a phase II block, following its rate of recovery, and assessing the effects of anti-ChE agents on recovery from phase II block.

## REFERENCES

1. Churchill-Davidson HC, Christie TH: The diagnosis of neuromuscular block in man. Br J Anaesth 31:290–301, 1959
2. Churchill-Davidson HC, Christie TH, Wise RP: Dual neuromuscular block in man. Anesthesiology 21:144–149, 1960
3. Katz RL, Wolf CE, Papper EM: The nondepolarizing neuromuscular blocking action of succinylcholine in man. Anesthesiology 24:784–789, 1963
4. Churchill-Davidson HC, Katz RL: Dual, phase II, or desensitization block? Anesthesiology 27:536–538, 1966
5. Katz RL, Ryan JF: The neuromuscular effects of suxamethonium in man. Br J Anaesth 41:381–390, 1969
6. Crul JF, Long CJ, Brunner EA, et al: The changing pattern of neuromuscular blockade caused by succinylcholine in man. Anesthesiology 27:729–735, 1966
7. Sokoll MD, Bastron RD: Duration of desensitization (phase 2) block after succinylcholine infusion. Anesth Analg 46:682–689, 1967
8. Lee C: Train-of-four fade and edrophonium antagonism of neuromuscular block by succinylcholine in man. Anesth Analg 55:663–667, 1976
9. Savarese JJ, Ali HH, Murphy JD, et al: Train-of-four nerve stimulation in the management of prolonged neuromuscular blockade following succinylcholine. Anesthesiology 42:106–111, 1975
10. Feldman SA, Tyrrell MF: A new theory of the termination of action of the muscle relaxants. Proc R Soc Med 63:692, 1970
11. Lee C, Chen D, Nagel EL, et al: Spontaneous recovery of the thumb twitch from neuromuscular block by suxamethonium in anaesthetized man. Br J Anaesth 48:91–95, 1976
12. Lee C: Dose relationships of phase II, tachyphylaxis and train-of-four fade in suxamethonium-induced dual neuromuscular block in man. Br J Anaesth 47:841–845, 1975
13. Lee C, Barnes A, Katz RL: Magnitude, dose requirement and mode of development of tachyphylaxis to suxamethonium in man. Br J Anaesth 50:189–194, 1978
14. Gissen AJ, Katz RL, Karis JH, et al: Neuromuscular block in man during prolonged arterial infusion with succinylcholine. Anesthesiology 27:242–249, 1966

ANESTH ANALG
59:117-122, 1980

# Nitroglycerin and the Neuromuscular Blockade Produced by Gallamine, Succinylcholine, *d*-Tubocurarine, and Pancuronium

**Silas N. Glisson, PhD,[*] Manuel M. Sanchez, MD,[†] Adel A. El-Etr, MD,[‡] and Rebecca A. Lim, MD[§]**

GLISSON, S. N., SANCHEZ, M. M., EL-ETR, A. A., AND LIM, R. A.: Nitroglycerin and the neuromuscular blockade produced by gallamine, succinylcholine, *d*-tubocurarine, and pancuronium. Anesth Analg 59:117–122, 1980.

The finding in cats of prolonged pancuronium neuromuscular blockade in conjunction with intravenous infusion of nitroglycerin was previously reported by this laboratory. To expand on this finding the present study compared the effects of nitroglycerin on neuromuscular blockade produced by gallamine, *d*-tubocurarine, succinylcholine, and pancuronium, and further characterized the nitroglycerin-pancuronium interaction. The results indicate that of the relaxants studied only pancuronium neuromuscular blockade is prolonged, and that the prolongation is not due to altered plasma elimination of pancuronium. In vitro pancuronium blockade was not affected by nitroglycerin, suggesting the involvement of a metabolite in the block prolongation response. Reversibility of the prolonged pancuronium block by neostigmine is not influenced by nitroglycerin.

**Key Words:** NEUROMUSCULAR RELAXANTS: pancuronium; PHARMACOLOGY: nitroglycerin.

CONTINUOUS intravenous infusion of nitroglycerin has recently been used as a means for decreasing cardiac pre- and afterload in patients undergoing coronary artery bypass operations.[1] In our early clinical experience with intravenous nitroglycerin for this purpose we noted prolongation of pancuronium neuromuscular blockade in a patient receiving nitroglycerin infusion. This nitroglycerin-pancuronium interaction was confirmed experimentally in cats.[2]

To expand on these findings, we undertook the present study to: (1) investigate and compare the effects of intravenous nitroglycerin on neuromuscular blockade produced by commonly used relaxants, i.e., gallamine, *d*-tubocurarine, succinylcholine, and pancuronium; (2) determine whether the prolongation of pancuronium block was due to a decreased clearance of plasma pancuronium; (3) compare in vivo and in vitro pancuronium doses needed to produce 50% muscle blockade in the presence and absence of nitroglycerin infusion; and (4) determine the reversibility of the prolongation of pancuronium blockade produced by nitroglycerin.

## Methods and Materials

Adult male cats were used in the in vivo experiments. Approval from the Institutional Committee on

---

[*] Associate Professor, Departments of Anesthesiology and Pharmacology.

[†] Senior Resident, Department of Anesthesiology Currently Staff Anesthesiologist, St. Mary's Hospital, Kankakee, Illinois.

[‡] Professor and Chairman, Department of Anesthesiology.

[§] Assistant Professor, Department of Anesthesiology.

Supported in part by USPHS grant RR05368.

Received from the Department of Anesthesiology, Loyola University Stritch School of Medicine, 2160 South First Ave., Maywood, Illinois 60153. Accepted for publication October 21, 1979. Presented at the Annual Meeting of the International Anesthesia Research Society, March 11-15, 1979, Hollywood, Florida.

Reprint requests to Dr. Glisson.

Animal Care was obtained. All cats were prepared in an identical manner. Anesthesia was provided using alpha-chloralose, 60 mg/kg IP. A tracheostomy was performed and with mechanical ventilation $Pa_{CO_2}$ maintained between 35 to 40 torr throughout the experiment. A cannula was placed in the carotid artery through which arterial blood pressure was monitored. The external jugular vein was cannulated for administration of intravenous fluids and drugs. The left gastrocnemius muscle and sciatic nerve were isolated and connected to a force displacement transducer and a Grass S44 nerve stimulator, respectively, to measure the muscle response.[2, 3] Supramaximal stimuli of 0.2 Hz and 0.2-msec duration were used for nerve stimulation. Muscle contractions were recorded on a Hewlett-Packard oscillographic recording system. Twitch amplitude was measured directly from metrically calibrated recording paper. The absence of a recordable twitch response was taken to indicate complete muscle paralysis; complete recovery from the block was taken to be the time when the twitch height equaled the pre-block control height. Lead II electrocardiogram was monitored using standard needle electrodes. Body temperature, blood gas tensions and electrolytes, and urine output were measured throughout the experiments. All remained within normal ranges.

To study the effect of nitroglycerin infusion on neuromuscular blockade produced by commonly used relaxants two groups of cats were used, control and experimental. The control group received continuous intravenous infusion of 5% dextrose in water (D5W) at the rate of 0.03 ml/kg/min. After 1 hour of infusion, either pancuronium (0.126 mg/kg), succinylcholine (0.05 mg/kg), *d*-tubocurarine (0.312 mg/kg), or gallamine (1.83 mg/kg) was injected as an intravenous bolus. Preliminary experiments established these relaxant doses as being approximately equipotent in the cat. The maximum degree of neuromuscular blockade and the time from drug injection to 100% twitch recovery were recorded. In addition, twitch height was recorded at 1-minute intervals from the first measurable sign of twitch recovery until complete recovery had occurred. A minimum of four cats were used for each relaxant.

The experimental group was treated in an identical manner, except that in place of the D5W, continuous intravenous infusion of nitroglycerin (32 μg/ml) was used at the rate of 1.0 μg/kg/min. A minimum of four cats were used for each relaxant.

Plasma pancuronium levels were measured in two additional groups of cats, treated the same as above, one group (N = 4) receiving pancuronium during infusion of D5W and the other pancuronium during infusion of nitroglycerin (N = 5). The pancuronium levels were measured at various times during the muscle blockade beginning 1 minute after the maximum degree of blockade had been achieved. The fluorometric method of Kersten et al[4] was used to measure the plasma pancuronium.

The dose of pancuronium needed to produce a 50% neuromuscular block in the presence and absence of nitroglycerin infusion was determined in both in vitro and in vivo preparations. For the in vitro preparation, 20 experiments were carried out using the standard isolated rat phrenic nerve-diaphragm preparation.[5] The phrenic nerve was stimulated supramaximally at a rate of 1.0 Hz and a duration of 0.2 msec; the twitch height was recorded oscillographically. The concentrations of pancuronium (micrograms per 50-ml bath) needed to produce a 50% neuromuscular blockade were measured in the presence of nitroglycerin concentrations in the bath of 0.00, 0.0064, 0.064, 0.64, and 6.40 μg/ml (N = 4 each). For the in vivo preparation, eight experiments were carried out using the intact cat sciatic nerve-gastrocnemius muscle preparation described above. The micrograms per kilogram of pancuronium needed to produce a 50% neuromuscular blockade was determined in the absence (N = 4) and presence of nitroglycerin infusion, 1.0 μg/kg/min (N = 4). Twitch recovery was recorded at 1-minute intervals from the time when recovery from the block first began until complete recovery had occurred.

In additional cat experiments tetanic fade and post-tetanic potentiation (N = 4) and neostigmine reversal (N = 4) were studied. Tetany was produced using supramaximal stimulation at 50 and 100 Hz and 0.2-msec duration. Neostigmine at a dose of 0.05 mg/kg mixed with atropine (0.02 mg/kg) was given when recovery from the nitroglycerin-prolonged block had reached 25%.

Statistical analysis of data was performed using the nonpaired "*t*" test. Recovery slope analysis was performed using linear regression and analysis of covariance. A probability less than 0.05 was considered to indicate a statistically significant difference.

## Results

The effect of nitroglycerin (NTG) on the duration of neuromuscular blockade produced in vivo by commonly used relaxants can be seen in Fig 1. NTG

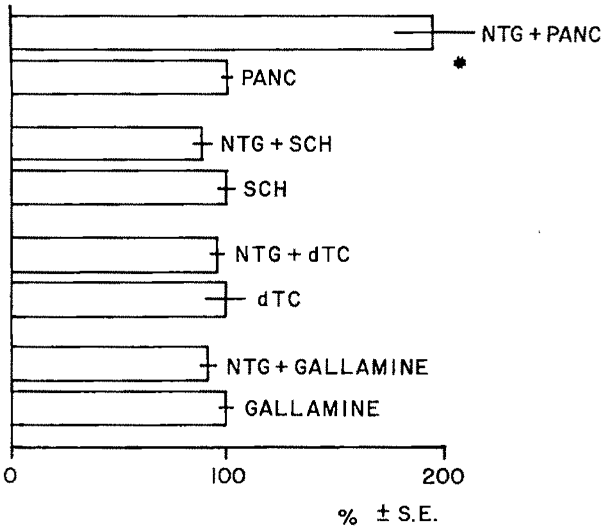


FIG 1. Effect of continuous intravenous infusion of nitroglycerin on the duration of neuromuscular blockade. Abscissa represents percent change in duration of neuromuscular blockade for each relaxant with nitroglycerin (NTG) infusion compared to blockade duration without nitroglycerin infusion (100%). Doses of relaxants were: pancuronium (PANC), 0.126; succinylcholine (SCH), 0.05; *d*-tubocurarine (dTC), 0.312; and gallamine, 1.83 mg/kg IV. Mean values are based on a minimum of four cats per group. Nitroglycerin, 1 μg/kg/min, had a significant effect only on pancuronium blockade; * $p < 0.02$.

infusion nearly doubled the duration of neuromuscular blockade produced by pancuronium (65 vs 127 minutes). This response was statistically significant ($p < 0.02$). Analysis of the blockade recovery slopes from these pancuronium experiments indicated that the rate of twitch recovery from the pancuronium blockade was significantly prolonged by infusion of NTG (Fig 2). NTG infusion did not significantly alter the duration of neuromuscular blockade produced by succinylcholine (10.2 vs 11.7 minutes), *d*-tubocurarine (44 vs 42 minutes), or gallamine (56 vs 51 minutes, Fig 1).

NTG infusion had no effect on the percentage of pancuronium cleared from plasma over a 120-minute time period beginning 1 minute after the maximum degree of neuromuscular blockade had been achieved (Fig 3). The plasma pancuronium level 1 minute after maximum blockade had been achieved was found to be 1.96 ± 0.22 μg/ml in the pancuronium group and 1.56 ± 0.13 μg/ml in the pancuronium plus NTG group. After 20 minutes of pancuronium blockade plasma pancuronium levels in both treatment groups decreased to 13% of their 1-minute levels. After 40 minutes of blockade the plasma pancuronium level dropped to 7%, at 80 minutes to 2%, and after 120 minutes, the last sampling time, to less than 1% of their 1-minute values. On a percentage basis, these elimination curves were found to be in close agreement with the plasma elimination curves of pancuronium reported by Agoston and Kersten.[6]

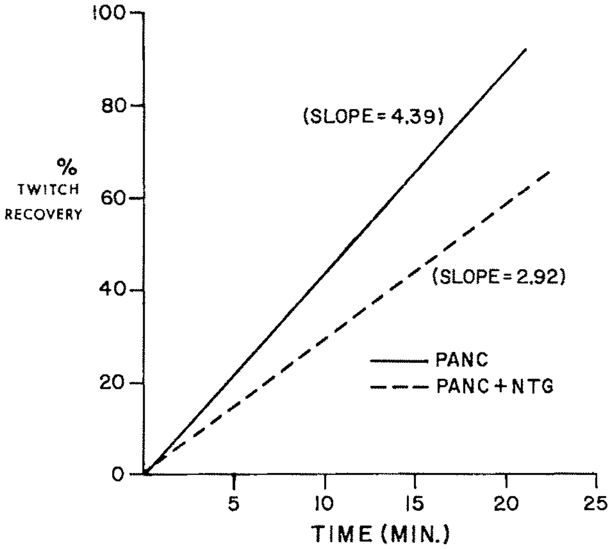


FIG 2. Regression analysis of in vivo muscle twitch recovery from (1) control pancuronium (PANC) neuromuscular blockade and (2) nitroglycerin (NTG) prolonged pancuronium blockade. Rate of recovery from muscle blockade produced by pancuronium, 0.126 mg/kg, was found to be significantly slowed during the infusion of nitroglycerin, 1 μg/kg/min ($p < 0.05$). Four cats were used per group.

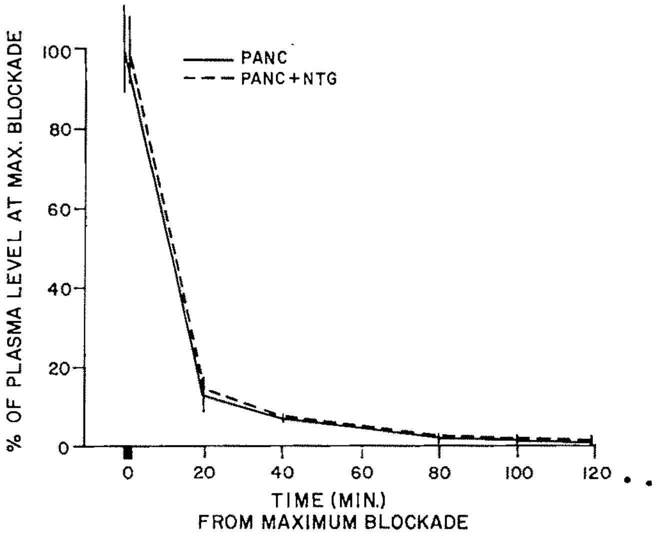


FIG 3. Effect of intravenous nitroglycerin (NTG), 1 μg/kg/min, on the clearance of pancuronium (PANC) from plasma. Average values ± SEM are based on a minimum of four cat experiments per group, each cat receiving 0.126 mg/kg IV of pancuronium. Time zero plasma pancuronium levels were obtained 1 minute after maximum block was achieved. The two plots were not statistically different.

Results from the in vitro rat diaphragm experiments demonstrated that the amount of pancuronium needed to produce a 50% muscle block with and without NTG present was the same, 43 ± 0.01 and 42.8 ± 0.48 µg/50-ml bath, respectively. Final concentrations of NTG in the bath ranged from none (0.00) to 6.40 µg/ml.

In in vivo cat experiments the micrograms per kilogram of pancuronium needed to produce a 50% block was found to be decreased during infusion of NTG (Table). Analysis of the blockade recovery slopes obtained in these experiments indicated that the rate of recovery from 50% neuromuscular blockade with and without NTG infusion was not statistically different ( $p > 1.0$, Fig 4).

During the prolonged portion of the pancuronium-NTG neuromuscular blockade, tetanic stimulation of the sciatic-gastrocnemius preparation demonstrated the presence of tetanic fade and post-tetanic twitch potentiation, and the administration of neostigmine (0.05 mg/kg) mixed with atropine (0.02 mg/kg) readily reversed the neuromuscular block (Fig 5).

## Discussion

The results of this study demonstrate that in the cat the prolongation by intravenous nitroglycerin of pancuronium neuromuscular blockade, previously reported by our group, does not occur when neuromuscular blockade is produced by gallamine, *d*-tubocurarine, or succinylcholine. Thus the nitroglycerin interaction appears selective for pancuronium. In a related study, Graham and Walts[7] recently completed an investigation in man on the effect of sodium nitroprusside-induced hypotension on the duration of action of neuromuscular blockade produced by pancuronium and *d*-tubocurarine. Their results show no difference in the duration of either pancuronium or *d*-tubocurarine neuromuscular blockade during sodium nitroprusside infusion. In light of their findings, it would appear that the prolongation of pancuronium neuromuscular blockade observed with nitroglycerin

**TABLE**

**Average Pancuronium Dose Needed to Produce 50% Neuromuscular Blockade in Vivo***

| | N | Dose | *p* value |
|---|---|---|---|
| Pancuronium | 4 | 20.2 ± 0.7 | <0.06 |
| Pancuronium + nitroglycerin | 4 | 14.7 ± 2.3 | |

* Values are means ± SEM.

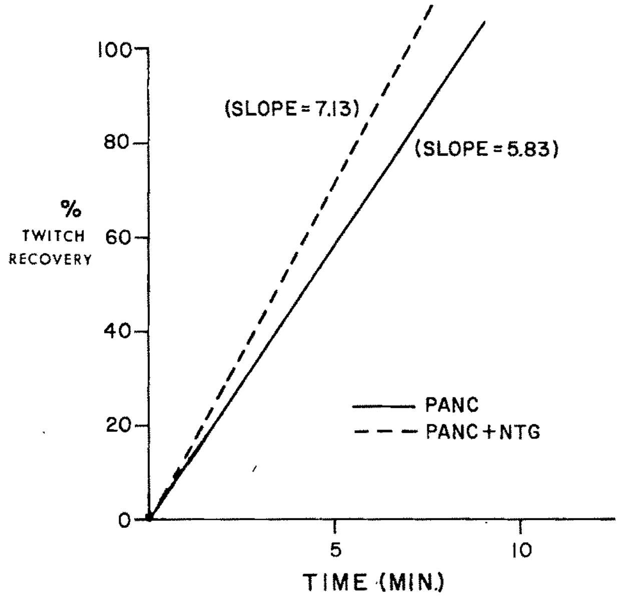


FIG 4. Regression analysis of in vivo muscle twitch recovery from 50% neuromuscular blockade produced by pancuronium (PANC). Nitroglycerin (NTG) infusion at the rate of 1 µg/kg/min had no significant effect on the rate of recovery from the block ($p > 1.0$). Four cats were used per group.

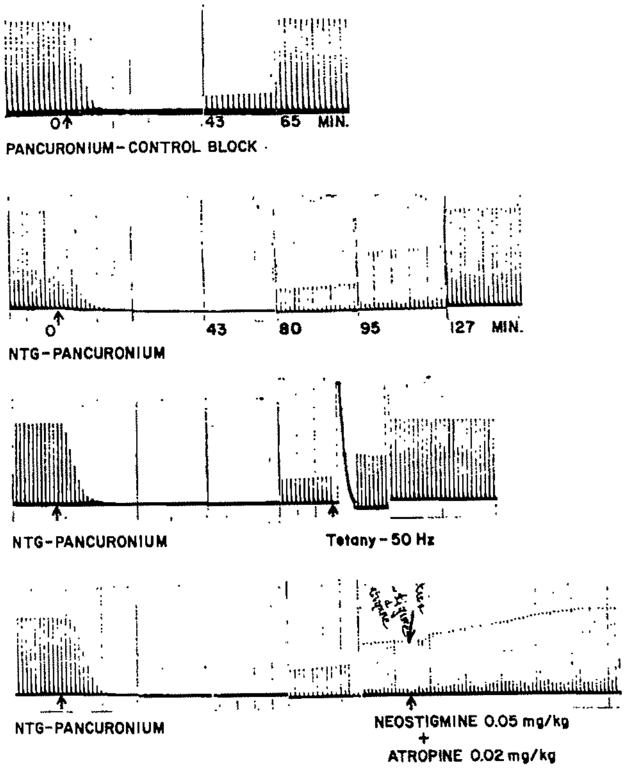


FIG 5. Composite twitch tracings for typical control pancuronium and nitroglycerin prolonged pancuronium blockade. Effect of tetanic stimulation and neostigmine on muscle twitch during block prolongation (90 to 100 minutes) are shown.

is not an effect common to all directly acting vasodilators.

To extend our evaluation of the nitroglycerin-pancuronium interaction we investigated the possibility that the observed block prolongation might be due to a decrease in the plasma elimination of pancuronium by nitroglycerin. This would, in effect, slow the rate of pancuronium dissociation from the neuromuscular receptors and cause prolongation of the pancuronium block. However, the finding that pancuronium elimination from plasma, measured over a period of 120 minutes beginning 1 minute after the maximum pancuronium blockade had been achieved, was not statistically different with and without nitroglycerin infusion rules out the possibility that nitroglycerin interfered with clearance of pancuronium from plasma. Further, the lack of effect of nitroglycerin on gallamine blockade, gallamine being eliminated unchanged by the kidneys,[8] suggests that renal excretion of relaxants is not impaired by nitroglycerin.

Another explanation for the prolongation of pancuronium blockade is that localized muscle blood flow was increased by the nitroglycerin causing a greater uptake and concentration of pancuronium in muscle with a resultant decrease in plasma pancuronium level.[9] If greater uptake of pancuronium into muscle did occur, it was not directly measurable by our methods. The fact that less pancuronium was found in plasma of animals given nitroglycerin 1 minute after achieving maximum blockade than in animals not given nitroglycerin supports this concept. If, however, nitroglycerin increases pancuronium distribution within muscle leading to a higher concentration of pancuronium at the neuromuscular junction and thus prolonged blockade, then why did block prolongation not occur with *d*-tubocurarine and gallamine? It is possible that the observed decrease in the plasma pancuronium level at 1 minute in the nitroglycerin group simply reflects a greater initial urinary excretion of pancuronium and not greater uptake into muscle. Pancuronium has been shown to have an initial rapid urinary excretion phase which may have been increased by nitroglycerin.[10] Unfortunately urinary levels of pancuronium were not measured in this study. These questions must be resolved by future experimentation.

We also examined whether nitroglycerin increased the magnitude of the pancuronium blockade, and whether it altered the recovery from the blockade. Our initial observations[2] suggested that it was the recovery portion of the pancuronium block that was prolonged by the nitroglycerin. Recovery slope analysis of the nitroglycerin-prolonged pancuronium block confirmed that recovery from the block was significantly slowed by nitroglycerin. The results from the cat experiments in which 50% neuromuscular blockade was produced by pancuronium demonstrated that nitroglycerin also increased the degree of neuromuscular blockade produced by pancuronium. These two findings suggest that nitroglycerin may be associated with increased affinity of receptors for pancuronium. In this connection, other drugs such as halothane have been shown to influence both the magnitude of response to pancuronium and the duration of effect, with a greater effect on the latter.[11] Pancuronium has pre- as well as postjunctional actions.[12, 13] Prejunctionally, pancuronium decreases release of acetylcholine from motor nerve terminals. Although this action normally contributes little to the overall muscle blockade produced by pancuronium, potentiation of the prejunctional effect by nitroglycerin could account for prolongation of the block. The lack of effect of nitroglycerin on pancuronium block in the isolated tissue preparation raises the possibility that a metabolite of nitroglycerin, or of pancuronium, might be involved. What must now be determined is the nitroglycerin dose in man at which pancuronium blockade is affected. Importantly, our results show that even during the prolongation of neuromuscular blockade produced by nitroglycerin, neostigmine rapidly and completely reversed the muscle paralysis.

In summary, this study has demonstrated in cats a selective drug interaction between intravenous nitroglycerin and pancuronium causing pancuronium neuromuscular blockade to be increased in both degree and duration. The mechanism of this interaction remains unknown. It is not due to altered plasma clearance of pancuronium. The interaction between nitroglycerin and pancuronium does not, however, alter the non-depolarizing character or reversibility of pancuronium blockade.

## REFERENCES

1. Kaplan JA, Dunbar RW, Jones EL: Nitroglycerin infusion during coronary artery surgery. Anesthesiology 45:14–21, 1976
2. Glisson SN, El-Etr AA, Lim R: Prolongation of pancuronium-induced neuromuscular blockade by intravenous nitroglycerin infusion. Anesthesiology 51:47–49, 1979
3. Glisson SN, Fajardo L, El-Etr AA: Amitriptyline therapy increases electrocardiographic changes during reversal of neuromuscular blockade. Anesth Analg 57:77–83, 1978
4. Kersten UW, Meijer DKF, Agoston S: Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. Clin Chim Acta 44:59–66, 1973

5. University of Edinburgh, Department of Pharmacology: Pharmacological Experiments on Isolated Preparations. Edinburgh, E and S Livingston, 1970
6. Agoston S, Kersten UVW: The pharmacokinetics of the steroid muscle relaxants, in Anaesthesia and Pharmacology. Baltimore, Williams & Wilkins, 1976, pp 207–218
7. Graham CW, Walts LF: Nitroprusside alters pancuronium and tubocurarine duration? Anaesthesia, in press 1979
8. Feldman SA, Cohen EN, Colling R: The excretion of gallamine in the dog. Anesthesiology 30:593–598, 1969
9. Goat VA, Yeung ML, Blakeney C, et al: The effect of blood flow upon the activity of gallamine triethiodide. Br J Anaesth 48:69–73, 1976
10. Agoston S, Kersten UW, Meijer DKF: The fate of pancuronium bromide in the cat. Acta Anaesth Scand 17:129–135, 1973
11. Katz RL: Modification of the action of pancuronium by succinylcholine and halothane. Anesthesiology 35:602–606, 1971
12. Gergis SD, Dretchen KL, Sokoll MD, et al: Effect of pancuronium bromide on acetylcholine release. Proc Soc Exp Biol Med 139:74–76, 1972
13. Blaber LC: The prejunctional actions of some non-depolarizing blocking drugs. Br J Pharmacol 47:109–116, 1973

---

## Hemodynamic Effects of Intravenous Metoprolol

The hemodynamic effects of the cardioselective beta adrenergic blocking agent metoprolol, at a dose of 0.1 mg/kg of body weight administered intravenously, were studied in 10 patients undergoing routine cardiac catheterization. The beta adrenergic blocking effect of the drug was confirmed by a reduction (53%, $p < 0.001$) in the mean heart rate response to a challenge with isoproterenol, and by a reduction (73%, $p < 0.001$) in the isoproterenol-induced increase in the first derivative of left ventricular pressure (dP/dt). An intrinsic negative inotropic effect was shown by a 43% reduction ($p < 0.05$) in the response of mean left ventricular dP/dt when the heart rate was fixed by atrial pacing alone. With the combination of atrial pacing and isoproterenol, metoprolol produced a 48% reduction ($p < 0.01$) in the response of mean left ventricular dP/dt, resulting from both the intrinsic depressor effect and the beta adrenergic blocking effect on the rate-independent beta agonist activity of isoproterenol. There was no significant change in right atrial, femoral arterial, or left ventricular end-diastolic pressure. Metoprolol is an effective cardioselective beta adrenergic blocking agent that, under the conditions of this study, reduced catecholamine-induced increases in heart rate and left ventricular dP/dt without significant alteration in ejection fraction, preload, or afterload. (*Bourdillon PD, Canepa-Anson R, Rickards AF: Hemodynamic effects of intravenous metoprolol. Am J Cardiol 44:1195–1200, 1979*)

ANESTH ANALG
59:123-129, 1980

# Airway Responses in Normal Subjects following Topical Anesthesia with Ultrasonic Aerosols of 4% Lidocaine

**Thomas J. Gal, MD***

---

GAL, T. J.: Airway responses in normal subjects following topical anesthesia with ultrasonic aerosols of 4% lidocaine. Anesth Analg 59:123–129, 1980.

Airway dynamics were studied in seven healthy unanesthetized male subjects before and after topical anesthesia with ultrasonic aerosols of 4% lidocaine to assess the effects of this clinically useful technique on normal pulmonary function. Responses to the ultrasonic mist per se were evaluated by studies on separate days with physiologic saline. Significant increases in expiratory flow rates during maximal and partial expiratory flow-volume curves occurred in response to lidocaine. In contrast, flows during partial expiratory flow-volume curves were reduced following saline inhalation. Lung elastic recoil was unaffected by either aerosol. Results of single breath nitrogen washout and responses to breathing helium were unchanged following topical anesthesia with lidocaine, but the saline aerosol significantly increased the slope of phase III during nitrogen washout and volume of isoflow after breathing helium. These changes indicate that topical anesthesia of the airway with 4% lidocaine given as an ultrasonic aerosol produces mild bronchodilation in healthy subjects, whereas saline administered in the same fashion causes mild bronchoconstriction. The effects of both aerosols most likely represent direct action on the smaller peripheral bronchi.

**Key Words:** ANESTHETICS, Local: lidocaine; AIRWAY: lidocaine; LUNG FUNCTION, Function: lidocaine; ANESTHETIC TECHNIQUES, topical.

---

THE INSTILLATION of 4% lidocaine as an ultrasonic aerosol produces effective topical anesthesia for instrumentation of the airway[1,2] but the administration of aerosols in this fashion may have significant respiratory effects. Nonanesthetic aerosols delivered by ultrasonic nebulization have increased airway resistance in patients with obstructive lung disease[3] and in normal anesthetized patients whose tracheas have been intubated.[4,5] The aerosol mist appeared to stimulate airway receptors and cause bronchoconstriction.[6] The bitter lidocaine mist may also act as an irritant and initiate bronchoconstriction.[7] On the other hand, the effect of lidocaine on airway smooth muscle may result in bronchodilation.[8,9]

Although several studies have reported the effects of inhaled lidocaine on airway function in man,[7, 8, 10-12] no data are available following administration of lidocaine in a fashion that provides adequate topical anesthesia prior to instrumentation of the airway. The purpose of this study was to assess the effects of such a technique with 4% lidocaine on normal airway dynamics. The effects of the ultrasonic mist per se were evaluated by control studies using isotonic saline.

---

* Assistant Professor.

Supported in part by funds from the American Lung Association.
Received from the Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication October 20, 1979. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Oct 21-25, 1978, Chicago, Illinois.
Reprint requests to Dr. Gal.

## Methods

The seven healthy nonsmoking males who participated in the study were between the ages of 23 and 30 and had normal baseline pulmonary function. All subjects gave informed consent and the protocol was approved by the Human Studies Committee of the University of Virginia. Subjects were studied on two separate days and by random allocation received either saline or 4% lidocaine on each of these days. Aerosols were produced by an ultrasonic nebulizer (Mistogen). Subjects breathed the mists for 10 minutes through a mouthpiece connected directly to the nebulizer by 30 cm of 22-mm i.d. corrugated tubing. They were instructed to inspire slowly and deeply and to hold their breath for 1 to 2 seconds at the height of inspiration to increase particle deposition.[13] This method was chosen to stimulate the procedure that in our experience has produced sufficient anesthesia for awake endotracheal intubation when combined with occasional supplemental sprays from an atomizer.

Physiologic measurements were performed with subjects in the sitting position each day before treatment (control) and 5 minutes after each aerosol treatment. Forced vital capacity (FVC) and forced expiratory volume in 1 second ($FEV_1$) were measured with a low resistance, waterless rolling seal spirometer (model 840, Ohio Medical Products). The spirometer was calibrated with a 3-L super syringe and provided a volume accuracy ± 30 ml. The largest value for each was used provided the FVC curve from which the $FEV_1$ was obtained was within 200 ml of the largest FVC measured. All volumes were corrected to body temperature and pressure saturated with water vapor. Maximum effort-flow volume loops were obtained with the spirometer interfaced with a fast response X-Y recorder (Hewlett-Packard); peak inspiratory flow ($\dot{V}_I$ max) and peak expiratory flow ($\dot{V}_E$ max) were used in the results.

The function of the intrathoracic airways was further assessed by measurements of maximum expiratory flow-volume (MEFV) curves in which flow and volume were plotted simultaneously during a maximal forced expiration from total lung capacity (TLC) to residual volume (RV). MEFV curves from at least three efforts when FVC values were within 5% of each other were aligned at TLC and maximum values for expiratory flow recorded at 10% intervals of FVC. These were used to construct composite MEFV curves for each subject during each measurement. Largest values for flow were used to minimize the effects of excessive effort which may reduce flow by artifacts caused by gas compression.[14] Subjects also generated partial expiratory flow-volume (PEFV) curves by inspiring to about 60% of FVC rather than TLC and then forcing expiration.[15] This maneuver was followed by inhalation to TLC and a maximal forced expiration to RV to obtain a reference MEFV curve. Since RV was the same for both PEFV and this subsequent MEFV curve, flows on PEFV curves were quantitated at 10% intervals of FVC above RV.

MEFV curves were also obtained after subjects performed three full inspirations to TLC with a mixture of 80% helium and 20% oxygen. This less dense gas mixture produces increased flows unless obstruction of the small peripheral airways is present. The response to helium was determined by superimposing the MEFV curves obtained with air (curves were only compared if FVC with helium and air differed by less than 3%). When FVCs with air and helium were unequal, curves were matched at residual volume.[16] The point on the air curves at which the increased flow with helium became equal to and joined the flow on the air curve was identified as the volume of isoflow (V iso $\dot{V}$). This was expressed as a percentage of FVC above RV. For each experimental condition V iso $\dot{V}$ was calculated as the mean of three such comparisons.

A modification of the single breath nitrogen washout technique was used to measure closing volume.[17] Subjects inspired 100% oxygen from RV to TLC then immediately expired to RV keeping flow-rate as close to 0.5 L/sec as possible. Expired nitrogen concentration sampled at the mouthpiece by a rapid response analyzer (Hewlett-Packard model 57302A) was displayed on the Y-axis of the X-Y recorder and volume on the X-axis. Closing volume (CV) was defined as the volume at which an abrupt increase in expired nitrogen occurred and was expressed as the difference between this point and RV. CV was also expressed as a percentage of the vital capacity (CV/VC%). The slope of the phase III alveolar plateau was also calculated from a line of best fit from 30% of expired vital capacity to the onset of CV and expressed as percent change in nitrogen concentration per liter ($\Delta N_2\%/L$).[18] At least two tracings were obtained for each condition with time allowed between for mouth $N_2$ to return to normal. Values for CV and slope of phase III were obtained as the mean of at least two satisfactory tracings that agreed closely, i.e., with similar vital capacity, slow expiratory flow, and positive identification of the abrupt change in slope at CV.

Esophageal pressure was used as an index of pleural pressure and was measured by an esophageal balloon-catheter system. The balloon, which was 10 cm long and contained 0.5 ml of air, was passed into the midesophagus and connected to a differential pressure transducer (Validyne MP45 range ± 50 cm $H_2O$) by 100-cm long PE-200 tubing. The opposite port of the transducer was connected to a pressure tap in the mouthpiece. Transpulmonary pressure was expressed as mouth pressure minus esophageal pressure. Lung elastic recoil was estimated by quasi-static pressure volume curves. Transpulmonary pressure was simultaneously plotted against volume on the X-Y recorder while subjects inspired to total lung capacity and then exhaled slowly (0.2 L/sec) to residual volume. Individual pressure-volume curves were constructed as the mean of two correctly recorded curves with the greatest inspiratory volume.

Subjects were observed closely and electrocardiograms monitored during and after each aerosol inhalation. Although the design of the study was originally double blind, the obvious taste of saline and the bitter taste of lidocaine were easily recognized by subjects. Results were analyzed blindly, however. The changes following each aerosol were compared to baseline values obtained prior to each treatment by Student's *t*-test for paired data; $p < 0.05$ was considered statistically significant. All values in text and tables are expressed as means ± SE of the mean.

## Results

During the 10-minute period of inhalation subjects received between 7 and 9 ml of solution. The saline aerosol produced mild coughing after the initial breath in three of the seven subjects. All subjects coughed after the first two or three breaths of lidocaine, but this disappeared with further inhalation. After inhalation of lidocaine subjects noted an impaired ability to swallow, numbness of the tongue and oropharynx, and a husky character of voice which suggested vocal paresis. Three subjects described a feeling of obstruction during deep inspiration. Two subjects noted mild tinnitus but none complained of headache, drowsiness, or paresthesias during or after the inhalation. Heart rate and rhythm remained unchanged during and after administration of either aerosol. The manifestations of topical anesthesia persisted for 30 to 40 minutes. Measurements of pulmonary function were completed well within this period.

Neither aerosol produced significant changes in FVC or $FEV_1$. Although three subjects described a sense of inspiratory obstruction, this was not reflected by significant changes in peak inspiratory flow recorded in the maximum effort flow-volume loops. Peak expiratory flows were also unchanged from control. Comparison of mean MEFV curves (Fig 1) showed statistically significant increases in maximum expiratory flow at 60, 50, and 40% of FVC associated with lidocaine aerosol. Mean MEFV curves were unchanged following saline. Control flow rates recorded from partial expiratory flow-volume (PEFV) curves did not differ from flows on control MEFV curves between 50% of FVC and residual volume (Fig 2). Lidocaine significantly increased flow rates at all intervals on the PEFV curves ($p < 0.01$), but flow rates after saline were significantly less than control at 50, 40, 30, and 20% of FVC ($p < 0.05$).

Following lidocaine inhalation closing volume (CV) increased in one subject (subject 1) but was unchanged in all others. Neither the absolute value of CV, CV/VC%, nor the slope of phase III were altered significantly (Table). Changes in CV induced by saline were highly variable: in two subjects CV increased, in three it decreased, and in two no changes occurred. Thus, no significant difference from pretreatment values could be demonstrated after inhalation of saline. In contrast the mean slope of phase III increased significantly after saline. Despite this increase all post-treatment values remained within normal limits (<2% $N_2$/L).[18]

Lidocaine inhalation did not affect the normal response to helium breathing; V iso $\dot{V}$ was unchanged from control levels (Table). Saline, on the other hand, significantly increased mean V iso $\dot{V}$ ($p < 0.05$). The increase was most marked in the four subjects (subjects 1, 5, 6, and 7) who exhibited distinct increases in the phase III slope during nitrogen washout.

Lung elastic recoil was not altered significantly by either inhalation of aerosol (Fig 3). Recoil pressures at total lung capacity and the slopes of the pressure volume curves in the range of tidal volume were similar to pretreatment values.

## Discussion

The results of this study demonstrate that a clinically useful technique for producing topical anesthesia does not adversely affect airway function in normal subjects. However, the lidocaine mist, prior to anesthetizing the airway, produced irritation in most subjects as evidenced by coughing. Compared to normal subjects patients with obstructive airway disease

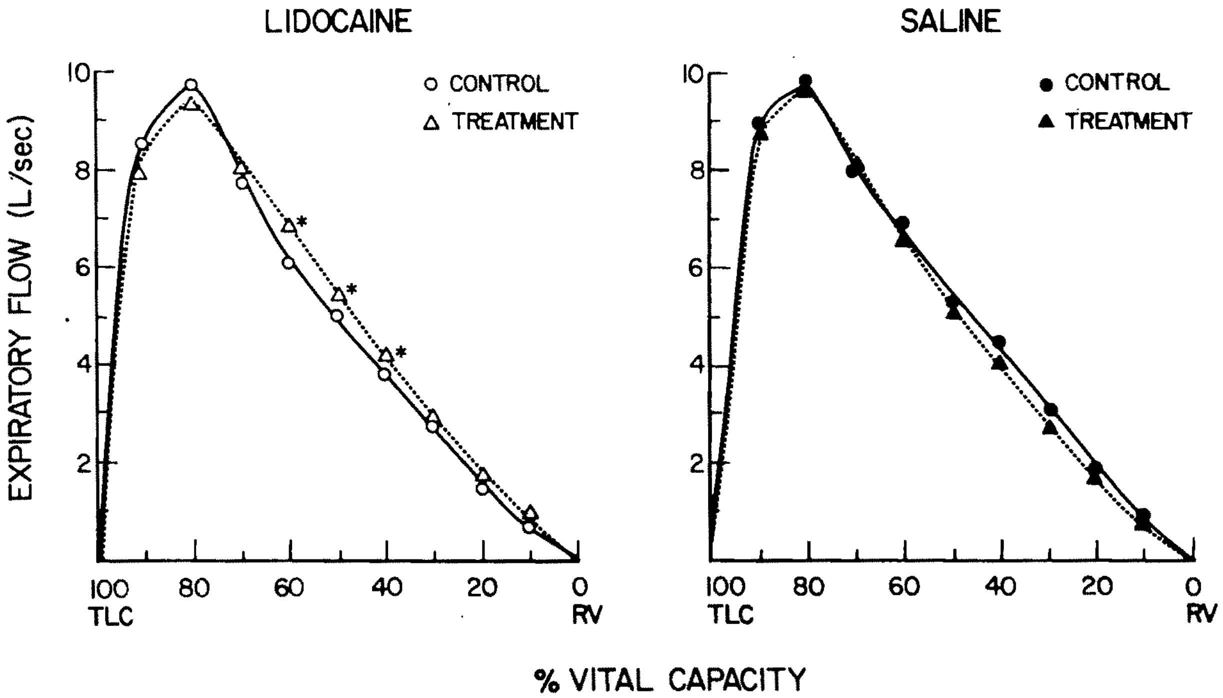


FIG 1. Maximum expiratory flow-volume curves before (control) and after treatment with ultrasonic aerosols of either 4% lidocaine or physiologic saline. Mean values for expiratory flows in seven subjects are plotted at 10% intervals of vital capacity between total lung capacity (TLC) and residual volume (RV). * $p < 0.05$ denotes values significantly different from control by paired "*t*" test.

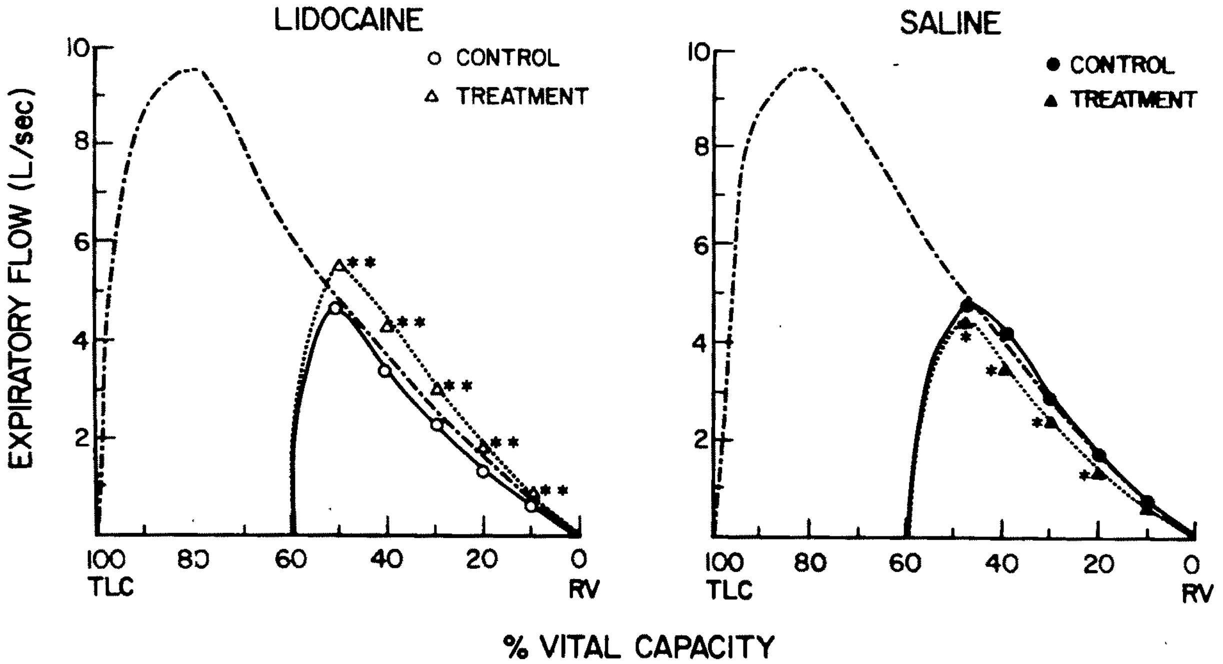


FIG 2. Partial expiratory flow-volume curves before (control) and after treatment with 4% lidocaine or physiologic saline administered as ultrasonic aerosols. Mean values for expiratory flow in seven subjects are plotted at 10% intervals of vital capacity above residual volume (RV). Control curves for maximal forced expiration initiated at total lung capacity (TLC) are plotted for comparison. * $p < 0.05$; ** $p < 0.01$ denotes values significantly different from control by paired "*t*" test.

**TABLE**

**Results of Single Breath Nitrogen Washout and Response to Helium Breathing before and after Inhalation of Ultrasonic Aerosols***

| | Control | Postlidocaine | Control | Postsaline |
|---|---|---|---|---|
| Closing volume (L) | 0.61 ± 0.07 | 0.64 ± 0.06 | 0.65 ± 0.07 | 0.60 ± 0.06 |
| CV/VC (%) | 10 ± 1 | 10.5 ± 1 | 10.7 ± 0.6 | 9.4 ± 1.0 |
| Slope of phase III ($\Delta N_2$%/L) | 1.16 ± 0.05 | 1.10 ± 0.04 | 1.16 ± 0.05 | 1.53 ± 0.10† |
| Volume of isoflow (% FVC) | 16 ± 1 | 15 ± 2 | 15 ± 2 | 23 ± 3† |

* Values are mean ± SE for seven subjects.
† $p < 0.05$ denotes significant difference when compared to control by paired '*t*' test.

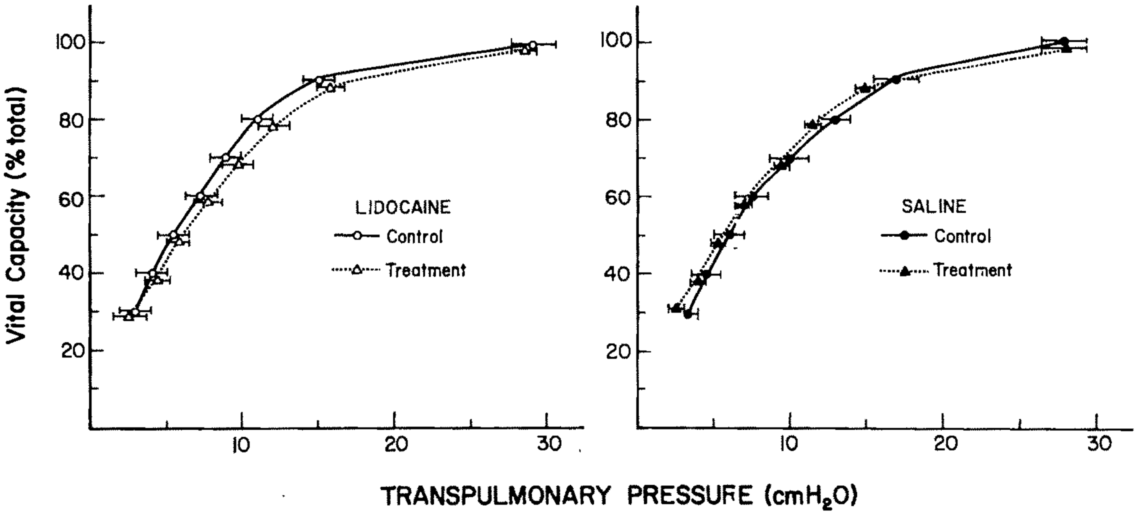


FIG 3. Mean deflation quasi-static pressure volume curves in seven subjects before (control) and after treatment with ultrasonic aerosols of 4% lidocaine or physiologic saline. Transpulmonary pressure is plotted at 10% intervals of vital capacity. Bars represent 1 SEM.

are more prone to develop reflex bronchoconstriction in response to many mild stimuli including inhaled agents. These reflex responses are immediate and would occur during the latent period prior to production of anesthesia by lidocaine.[19] Therefore, in such patients the immediate response to lidocaine inhalation is likely to be bronchoconstriction, although there is some evidence suggesting that subsequent bronchodilation occurs.[11]

Airway responses can be measured during submaximal flows such as during panting (airway resistance) or during the maximal effort of forced expiratory maneuvers. The latter were chosen for this study because they more directly reflect the properties of the lung and intrathoracic airways.[20] In contrast, measurements of airway resistance are profoundly influenced by the status of the upper airway (mouth to glottis). Variable effects on the upper airway may explain the inability to demonstrate systematic changes in airway resistance in normal subjects following topical anesthesia with another local anesthetic aerosol (5% bupivacaine).[21]

Measurements during maximal forced exhalations may not always demonstrate dramatic changes in airway tone because inhalation to total lung capacity reduces normal airway tone and may mask the effects of induced bronchodilation or bronchoconstriction.[22] This effect can be avoided if forced exhalations are begun at a lung volume below total lung capacity as in the case of PEFV curves. Flow measurements during PEFV curves are more sensitive to changes in airway tone than MEFV curves.[23] This is because prior to performing a PEFV maneuver, a subject inspires only to about 1.0 above FRC and does not produce bronchodilation as occurs when he inspires fully to TLC. Thus any bronchodilation (increased flow rates) or bronchoconstriction (decreased flow rates) will be more apparent on PEFV curves. In addition they possess the distinct advantage of being uninfluenced by the status of the upper airway.

Flow rates during MEFV curves after saline reflected insignificant changes but flows were reduced consistently on PEFV curves. Lung elastic recoil, the other important determinant of expiratory flow, was unchanged.[24] Therefore, the reduced flows resulted from increases in resistance in the small peripheral airways. Similarly, the lidocaine-induced increase in flow rates on PEFV curves reflects dilation in the same airways. The changes produced by lidocaine on MEFV curves were less dramatic at low lung volumes and may reflect solely the masking of airway responses produced by inhalation to total lung capacity. On the other hand, lidocaine may have dilated the larger intrathoracic airways as well as the smaller bronchi. In these airways smooth muscle tone increases wall stiffness and limits the extent to which these airways are dynamically compressed during maximal forced expirations. If this smooth muscle tone is reduced by bronchodilation, the airways become more compressible, collapse at lower transmural pressures, and limit maximal flow. This may explain why flow rates at low lung volumes decrease or fail to increase in normal subjects after bronchodilator drugs.[25] These same flows on MEFV curves failed to increase significantly in this study following lidocaine (Fig 1).

The volume of isoflow ($V$ iso $\dot{V}$) after breathing helium provides a sensitive index of airway dysfunction. When the principal site of obstruction is in the small peripheral airways, flow rates with the helium-oxygen mixture do not increase appreciably since the flow pattern in these airways is laminar and thus unaffected by the density of gases breathed. When there is a loss of lung elastic recoil or an increased resistance in the small peripheral airways, laminar flow predominates over a greater portion of the FVC and $V$ iso $\dot{V}$ increases.[16] The increased $V$ iso $\dot{V}$ noted after saline is compatible with small airway constriction since lung recoil was unaffected.

Measurements from single breath nitrogen washout used to measure closing volume are complex and difficult to interpret in terms of changes in airway function. An increased closing volume is usually interpreted as evidence of small airway obstruction. However, one subject in this study had an increased closing volume after lidocaine with, at the same time, increased flows on PEFV curves suggestive of bronchodilation. Increases in closing volume have been demonstrated following isoproterenol inhalation and thus are compatible with bronchodilation.[26]

The slope of the phase III alveolar plateau, i.e., the portion of the nitrogen washout curve that precedes the onset of closing volume, reflects the regional nonhomogenous pattern whereby different lung regions empty. Any process causing airway obstruction tends to increase the slope.[18] Following saline inhalation four subjects demonstrated distinct increases in phase III slopes. In all four the actual inflection points for the onset of the phase IV, or closing volume, were difficult to discern. It is also interesting that in three of the four, closing volume decreased after saline. The latter change is compatible with bronchoconstriction and a failure to establish the normal concentration gradient for nitrogen between apical and basal areas of lung.[27]

The apparent bronchoconstriction following saline was surprising because of the lack of subjective irritant effects. Although the reasons are not clear one may postulate that, because of the size of the particles generated by the ultrasonic nebulizer, this effect represents a direct action on the small bronchi. Another possible mechanism which must be considered relates to the actions of solutes such as sodium chloride, which tend to mobilize secretions. If not eliminated by coughing these secretions may cause airway obstruction. However, in the face of the small volume of solution administered, this is unlikely.

Possible mechanisms for the action of lidocaine include interruption of afferent receptors in the upper airway and direct action on the smooth muscle of the lower airways. The latter mechanism is more likely because of the particle size produced by the nebulizer. However, it is also possible that the effect was mediated systemically. Although blood levels of lidocaine were not measured in this study, similar applications of lidocaine have resulted in lidocaine levels averaging 1.5 $\mu$g/ml in arterial blood.[2] The presence of mild tinnitus suggested that this level was approached in at least two subjects in this study. Significant changes in airway function have not been demonstrated after doses of intravenous lidocaine likely to produce even higher blood levels.[8, 11] Because of this apparent lack of relationship with blood levels, it is unlikely that the airway responses noted in this study represent a systemic effect of lidocaine.

We conclude that administration of 4% lidocaine by ultrasonic nebulization to achieve topical anesthesia of the airway produced mild bronchodilation in healthy subjects. In contrast, saline administered in the same fashion caused bronchoconstriction. These effects most likely represent a direct effect on the smaller bronchi. Since the effects of lidocaine were mild, it is doubtful that administration of the aerosol could be used to produce clinically effective bronchodilation in patients with airway disease. The safety of ultrasonic nebulization of lidocaine used clinically to produce topical anesthesia of the airway in patients with airway disease requires further investigations.

## ACKNOWLEDGMENT

The author thanks Mr. Bruce Daggy for his excellent technical assistance.

## REFERENCES

1. Christoforidis AJ, Tomashefski JF, Mitchell RI: Use of an ultrasonic nebulizer for application of oropharyngeal, laryngeal, and tracheobronchial anesthesia. Chest 59:629–633, 1971
2. Karvonen S, Jokinen K, Karvonen P, et al: Arterial and venous blood lidocaine concentrations after local anaesthesia of the respiratory tract using an ultrasonic nebulizer. Acta Anaesth Scand 20:156–159, 1976
3. Cheney FW, Butler J: The effects of ultrasonically produced aerosols on airway resistance in man. Anesthesiology 29:1099–1106, 1968
4. Waltemath CL, Bergman NA: Increased respiratory resistance provoked by endotracheal administration of aerosols. Am Rev Respir Dis 108:520–525, 1973
5. Cheney FW, Butler J: Effects of ultrasonic aerosols on total respiratory resistance of the intubated patient. Anesthesiology 32:456–458, 1970
6. Nadel JA: Mechanism of airway response to inhaled substances. Arch Environ Health 16:171–174, 1968
7. Howard P, Cayton RM, Brennan SR, et al.: Lidocaine aerosol and persistent cough. Br J Dis Chest 71:19–24, 1977
8. Loehning RW, Waltemath CL, Bergman NA: Lidocaine and increased respiratory resistance produced by ultrasonic aerosols. Anesthesiology 41:306–310, 1976
9. Dain D, Boushey HA, Gold WM: Inhibition of respiratory reflexes by local anesthetic aerosols in dogs and rabbits. J Appl Physiol 38:1045–1050, 1975
10. Miller WC, Awe R: Effect of nebulized lidocaine on reactive airways. Am Rev Respir Dis 111:739–741, 1975
11. Weiss EB, Patwardman AV: The response to lidocaine in bronchial asthma. Chest 72:429–438, 1977
12. Fish JE, Peterman VI: Effects of inhaled lidocaine on airway function in asthmatic subjects. Respiration 37:201–207, 1979
13. Pavia D, Thompson ML, Clarke SW, et al.: Effect of lung function and mode inhalation on penetration of aerosol into the human lung. Thorax 32:194–197, 1977
14. Ingram RM, Schilder DP: Effect of gas compression on pulmonary pressure, flow, and volume relationship. J Appl Physiol 21:1521–1526, 1966
15. Bouhuys A: The Physiology of Breathing. New York, Grune & Stratton, Inc, 1977, p 215
16. Hutcheon M, Griffin P, Levinson H, et al.: Volume of isoflow, a new test in detection of mild abnormalities in lung mechanics. Am Rev Respir Dis 110:458–465, 1974
17. Buist AS, Ross BB: Predicted values for closing volumes using a modified single breath nitrogen test. Am. Rev. Respir Dis 107:744–752, 1973
18. Buist AS, Ross BB: Quantitative analysis of the alveolar plateau in diagnosis of early airway obstruction. Am Rev Respir Dis 108:1078–1087, 1973
19. Adriani J, Zepernick R, Arens J, et al.: The comparative potency and effectiveness of topical anesthetics in man. Clin Pharmacol Ther 5:49–62, 1964
20. Ingram RH, McFadden ER: Localization and mechanism of airway responses. N Engl J Med 297:596–600, 1977
21. Cross BA, Guz A, Jan SK, et al.: The effect of anesthesia of the airway in dog and man: a study of respiratory reflexes, sensations and lung mechanics. Clin Sci Mcl Med 50:439–454, 1976
22. Vincent NJ, Knudson R, Leith D, et al.: Factors influencing pulmonary resistance. J Appl Physiol 29:236–243, 1970
23. Bouhuys A, Hunt VR, Kim MB, et al.: Maximum expiratory flow rates in induced bronchoconstriction in man. J Clin Invest 48:1159–1168, 1969
24. Mead J, Turner JM, Macklem PT et al.: Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 22:95–108, 1967
25. Bouhuys A: Pulmonary response to bronchodilators. Am Rev Respir Dis 110(Suppl):119–124, 1974
26. Brooks SM, Barber MO: Changes in closing volume measurement after isoproterenol inhalation. Am Rev Respir Dis 109: 198–204, 1974
27. Benson MK, Newberg LA, Jones JG: Nitrogen and bolus closing volumes: differences after histamine induced bronchoconstriction. J Appl Physiol 38:1088–1091, 1975

ANESTH ANALG
59:130-139, 1980

# Comparison of Cardiovascular Responses to Anesthesia and Operation When Intravenous Lidocaine or Morphine Sulfate Is Used as Adjunct to Diazepam-Nitrous Oxide Anesthesia for Cardiac Surgery

**Paul R. Knight, MD, PhD,* Donald A. Kroll, MD, PhD,† Michael L. Nahrwold, MD,‡ J. Kenneth Denlinger, MD,§ Marvin Kirsh, MD,‖ Lee O. Welter, MD,¶ Anne G. Hill, MD,# Peter J. Cohen, MD,** and R. A. Ronfeld, PhD††**

---

KNIGHT, P. R., KROLL, D. A., NAHRWOLD, M. L., DENLINGER, J. K., KIRSH, M., WELTER, L. O., HILL, A. G., COHEN, P. J., AND RONFELD, R. A.: Comparison of cardiovascular responses to anesthesia and operation when intravenous lidocaine or morphine sulfate is used as adjunct to diazepam-nitrous oxide anesthesia for cardiac surgery. Anesth. Analg. 59:130–139, 1980.

Intravenous lidocaine was evaluated as an anesthetic adjunct and its hemodynamic effects compared to those of morphine sulfate. Forty patients undergoing surgery for coronary artery bypass or aortic valve replacement for moderate aortic stenosis were randomly assigned to one of two groups. Patients in group 1 received a total dose of 2 mg/kg of morphine sulfate while those in group 2 received 21 mg/kg of lidocaine. In addition, patients in both groups were given 0.6 mg/kg of diazepam and 50% $N_2O$ in oxygen.

Peak plasma lidocaine levels in group 2 occurred following sternotomy. Electroencephalographic evidence of seizure activity was absent at this time. Indices of myocardial performance (cardiac index, stroke work index) were depressed following induction of anesthesia and remained depressed up to institution of cardiopulmonary bypass in patients given lidocaine. Arterial blood pressure changed minimally. In contrast, patients given morphine demonstrated an increase in cardiac index and left ventricular stroke work index following tracheal intuba-

---

[*] Assistant Professor, Department of Anesthesiology; Assistant Research Scientist, Department of Epidemiology.

[†] Resident, Department of Anesthesiology.

[‡] Associate Professor, Department of Anesthesiology.

[§] Associate Professor, Department of Anesthesiology, University of California-San Diego.

[‖] Professor, Department of Surgery, Thoracic Division.

[¶] Instructor, Department of Anesthesiology.

[#] Assistant Professor, Department of Anesthesiology.

[**] Chairman and Professor, Department of Anesthesiology.

[††] Head, Drug Disposition, ASTRA Research Laboratories, Framingham, Massachusetts.

Supported by the Maximum Development Fund of the Department of Anesthesiology, University of Michigan Medical Center.

Received from the Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan. Accepted for publication October 25, 1979.

Reprint requests to Dr. Knight, University of Michigan Hospital, Department of Anesthesiology, Ann Arbor, MI 48109.

tion. Arterial blood pressure and systemic vascular resistance initially decreased following induction of anesthesia and increased with tracheal intubation in patients receiving morphine sulfate. Arterial blood pressure, stroke work index, and systemic vascular resistance increased further in these patients while cardiac index returned to control values during the period of surgical stimulation.

Electrocardiographic changes indicative of myocardial ischemia did not differ in the two groups. The relationship between myocardial oxygen supply and demand, as reflected by the rate pressure product and endocardial viability ratio indices, was, however, adversely affected during surgical stimulation in the patients given morphine.

Lidocaine produced stable clinical anesthesia without large fluctuations in hemodynamic function. In contrast to morphine, lidocaine depressed the hypertensive and tachycardic responses to surgery, thus favorably influencing the balance between myocardial oxygen supply and demand.

**Key Words:** ANESTHETICS, Intravenous: morphine and lidocaine; ANESTHETICS, Local: lidocaine; ANALGESICS, Narcotic: morphine; ANESTHESIA: cardiovascular; SURGERY: cardiovascular.

IN PATIENTS with coronary artery disease or left ventricular hypertrophy due to aortic stenosis, myocardial perfusion is often inadequate to tolerate an increase in oxygen demand produced by the hypertensive and tachycardic responses that may accompany tracheal intubation[1-5] or surgical manipulation. Stimulation of the patient during laryngoscopy and surgery frequently produces electrocardiographic findings of ST and T wave changes suggestive of myocardial ischemia.[6] In addition, laryngeal reflexes during tracheal intubation often are the cause of arrhythmias.[6-10] Therefore, in patients with ischemic heart disease, optimal anesthesia care requires that stressful reflex responses to airway manipulation and surgical stimulation be minimized. This must be accomplished without undue depression of myocardial function.

Intravenous lidocaine may be useful in achieving these goals. Lidocaine produces central sedation, suppresses autonomic reflexes,[a] and may protect the ischemic myocardium from ultrastructural damage associated with high circulating catecholamine levels.[11] Previous work shows that lidocaine can attenuate the noxious reflexes associated with tracheal intubation when used topically[12-14] or intravenously.[15, 16, a] However, inhibition of the increase in heart rate seen with tracheal intubation requires relatively high doses of intravenous lidocaine (6 mg/kg).[b] Lidocaine in these doses has negative inotropic effects.[17] The present study evaluates the circulatory responses during open-heart surgery performed when high-dose intravenous lidocaine is added to diazepam-nitrous oxide anesthesia and compares these responses to those observed when morphine is added to diazepam-nitrous oxide anesthesia.

## Methods

Forty adult patients undergoing anesthesia for either elective aortic valve replacement for moderate aortic valve stenosis (16 patients) or coronary artery bypass grafts (24 patients) comprised the study group. All patients had ejection fractions greater than 50%. The experimental protocol was approved by the Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan.

Under local anesthesia, a radial arterial catheter was placed for continuous monitoring of systemic arterial pressure. A Swan-Ganz catheter was positioned in the pulmonary artery by way of the right internal jugular vein for measurement of cardiac output and central venous and pulmonary arterial wedge pressures. Systemic and pulmonary arterial pressures were continuously recorded throughout the operation. In addition, a fast trace at 100 mm/sec of the arterial pressure was obtained for calculation of the endocardial viability ratio. Lead II and V5 of the electrocardiogram was continuously recorded and a bipolar (frontal-occipital) electroencephalogram was monitored for evidence of seizure activity.

The patients were randomly assigned to one of two groups. All patients received 10 mg of morphine sulfate and 0.4 mg of scopolamine intramuscularly 1 hour prior to arrival in the operating room. Patients in group 1 received intravenous morphine sulfate up to a total dose of 2 mg/kg during anesthesia and surgery. Patients in group 2 received intravenous lidocaine up to a total dose of 21 mg/kg during anesthesia and surgery. Other medication including digitalis, diuretics, and propranolol was continued until the day of surgery. Neither the type of surgery nor the type and frequency of the drugs used preoperatively differed significantly in the two groups.

---

[a] Denlinger JK, Messner JT, D'Orazio DJ: Effect of intravenous lidocaine on the circulatory response to tracheal intubation (abstract), presented to the American Society of Anesthesiologists, October 13, 1975.

[b] Falk RB, Denlinger JK, Foley WT: Hemodynamic responses during lidocaine-diazepam-$N_2O$ anesthesia in cardiac surgical patients (abstract), presented to the American Society of Anesthesiologists, October 24, 1978.

Anesthesia was induced slowly over the course of 15 minutes with the patient initially breathing 100% oxygen. Diazepam, 0.6 mg/kg, and either 0.5 to 1 mg/kg of morphine sulfate (group 1) or 6 mg/kg of lidocaine containing no preservative (group 2) were given incrementally until the patient failed to respond to verbal commands and lost the eyelid reflex. At this time 50% nitrous oxide in oxygen was started in both groups of patients. Pancuronium bromide, 0.15 mg/kg, was used to facilitate tracheal intubation and anesthesia was maintained with a maximum total dose of 2 mg/kg of morphine sulfate (mean total morphine dose, 121 ± 12 mg (SEM)), in group 1, or with a maximum total dose of 21 mg/kg of lidocaine (mean total lidocaine dose, 1373 ± 202 (SEM)) in group 2. Both drugs were administered to the total dose unless the systolic arterial blood pressure decreased more than 20% of awake values. All patients were mechanically ventilated to maintain a $Pa_{CO_2}$ between 30 to 35 torr during anesthesia and surgery.

The following derived hemodynamic parameters were determined: rate pressure product (RPP in mm Hg beats/min), systemic vascular resistance (SVR in $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$), cardiac index (CI in L/min/$m^2$), stroke volume index (SVI in ml/beat/$m^2$) and left ventricular stroke work index (LVSWI in $g\cdot m/m^2$). Body surface area (BSA in $m^2$) was obtained from a nomogram using height and weight. The derived data were determined using the following formula in which CO is cardiac output (L/min), HR is heart rate (beats/min), MAP is mean arterial blood pressure (torr), CVP is central venous pressure (torr), and PCWP is pulmonary capillary wedge pressure (torr):

$$CI = \frac{\text{CO (L/min)}}{\text{BSA } (m^2)}$$

$$\text{RPP} = \text{HR (beats/min)} \times \text{systolic arterial blood pressure (mm Hg)}$$

$$\text{SVI (ml/beat/m}^2) = \frac{CI}{HR}$$

$$\text{SVR } (\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}) = \frac{(\text{MAP} - \text{CVP}) \times 80}{\text{CO}}$$

$$\text{LVSWI } (g\cdot m/m^2) = \text{SVI} \times (\text{MAP} - \text{PCWP}) \times 0.0136$$

The endocardial viability ratio (EVR) was determined by dividing the diastolic pressure time index (the area under the diastolic portion of the systemic pressure curve minus the area under the filling pressure) by the systolic tension time index (the area under the systolic portion of the systemic pressure curve).[18, 19] An EVR with a value less than 0.7 is considered evidence of inadequate endocardial oxygen delivery especially when arterial oxygen content is decreased. Values less than 0.4 are definitely indicative of compromised endocardial perfusion.[20] Since the hematocrit did not change significantly prior to cardiopulmonary bypass, and since arterial oxygen saturation was 99% or greater with a 50% $F_{IO_2}$, these values were not corrected for arterial oxygen content.

Hemodynamic measurements were made following the insertion of cannulae prior to induction of anesthesia, immediately prior to and immediately following tracheal intubation, prior to skin incision, following sternotomy, and prior to and following cardiopulmonary bypass. Plasma lidocaine levels were determined in arterial blood samples obtained after cannulation was complete, after tracheal intubation, after sternotomy, and before and after cardiopulmonary bypass. In addition a small specimen of atrial appendage was obtained for analysis of myocardial tissue lidocaine levels at the same time the arterial sample for blood levels was obtained. These samples were taken just before initiation of cardiopulmonary bypass. Lidocaine levels were assayed according to the method of Keenaghan.[21]

All data were statistically analyzed using the Michigan Interactive Data Analysis System (MIDAS). This computerized data system, which allows the analysis of both analytical and categorical variables, was used to provide a two-way analysis of variance to test whether the measured and derived variables had changed with time. Specific comparisons were made using Student's *t*-test for paired and unpaired data. All data are expressed as means ± SEM.

## Results

### Anesthesia Alone

In group 1 (morphine), mean heart rate (Fig 1) increased 11 beats/min with induction of anesthesia from 66 to 77 beats/min ($p < 0.05$). Laryngoscopy and intubation were associated with a further increase of 9 beats/min ($p < 0.05$). Prior to incision the heart rate had returned to control values. Systolic arterial blood pressure decreased 37 torr ($p < 0.01$) following induction from 141 torr to 104 torr (Fig 2) but increased to preinduction levels following tracheal intubation. Prior to skin incision systolic arterial blood pressure was again at postinduction (preintubation) levels. Cardiac index (Fig 3) increased above awake levels during induction of anesthesia prior to tracheal intubation and remained significantly elevated following tracheal intubation. The increases in cardiac index observed following induction of anesthesia and tracheal intubation were not accompanied by statistically significant changes in pulmonary capillary wedge pressure (Fig 4). Following tracheal intubation, however, pulmonary capillary wedge pressures decreased prior to incision significantly ($p < 0.05$) below levels observed prior to tracheal intubation. Systemic vascular resistance (Fig 5) and left ventricular stroke work index (Fig 6) decreased following induction of anesthesia ($p < 0.01$) and increased back to awake levels briefly during tracheal intubation ($p < 0.05$). Both then decreased again prior to skin incision.

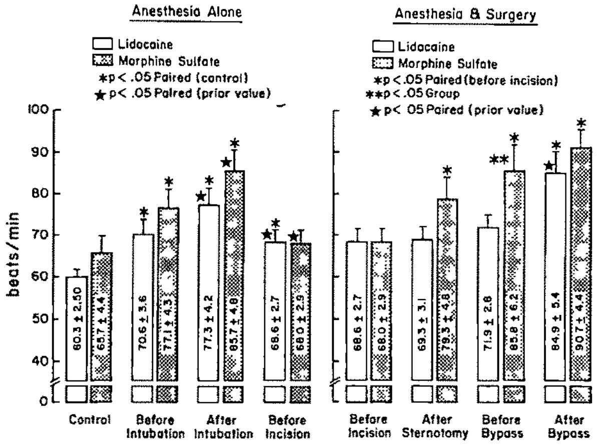


FIG 1. Heart rate during anesthesia, intubation, and surgery (mean ± SEM).

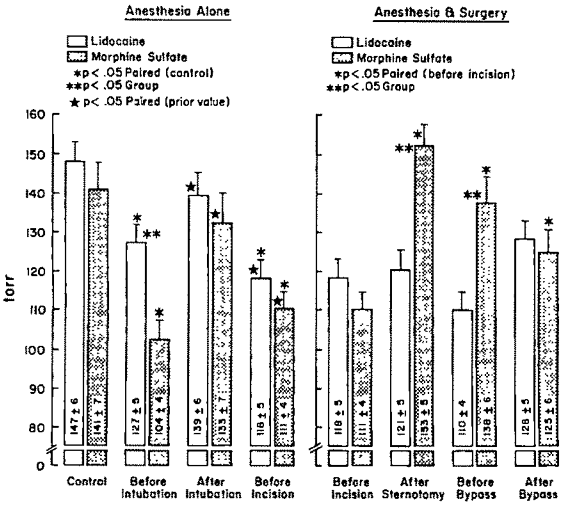


FIG 2. Systolic arterial blood pressures during anesthesia, intubation, and surgery (mean ± SEM).

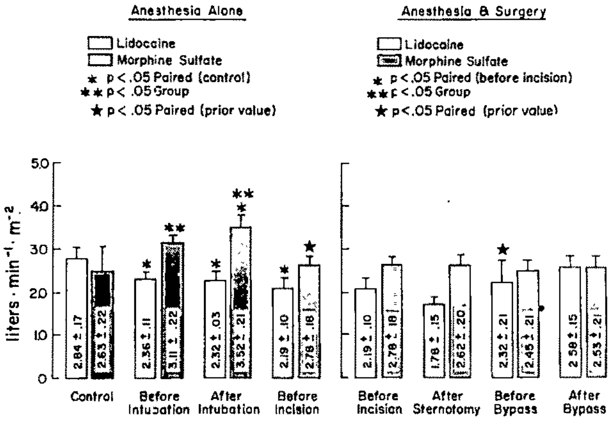


FIG 3. Cardiac indices during anesthesia, intubation, and surgery (mean ± SEM).

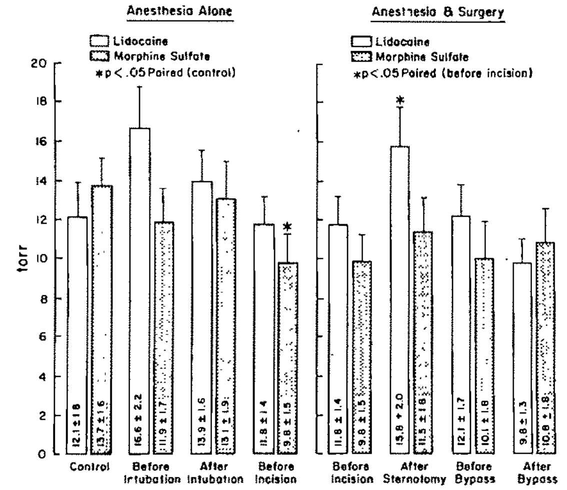


FIG 4. Pulmonary capillary wedge pressures during anesthesia, intubation, and surgery (mean ± SEM).

The two indices of the relationship between myocardial oxygen supply and demand, rate pressure product (Fig 7) and endocardial viability ratio (Tables 1 and 2), increased ($p < 0.05$) and decreased significantly ($p < 0.05$), respectively, compared to control following tracheal intubation. They then returned to awake control levels prior to skin incision.

In group 2 (lidocaine), lidocaine plasma levels averaged 6.43 μg/ml following induction of anesthesia and tracheal intubation (Fig 8). Heart rate (Fig 1) did not differ from the pattern seen in patients given morphine. Systolic arterial blood pressure (Fig 2) decreased 20 torr with induction of anesthesia ($p < 0.05$). This decrease was significantly less than in patients given morphine ($p < 0.01$). Following tracheal

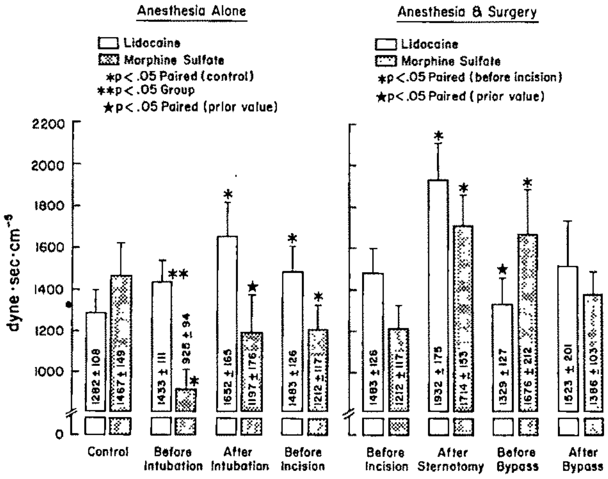


FIG 5. Systemic vascular resistance during anesthesia, intubation, and surgery (mean ± SEM).

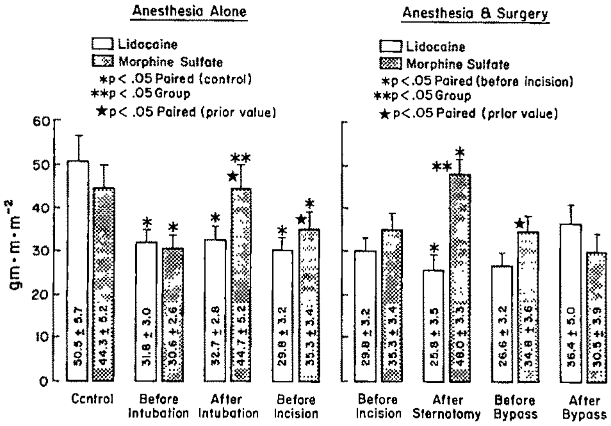


FIG 6. Left ventricular stroke work indices during anesthesia, intubation, and surgery (mean ± SEM).

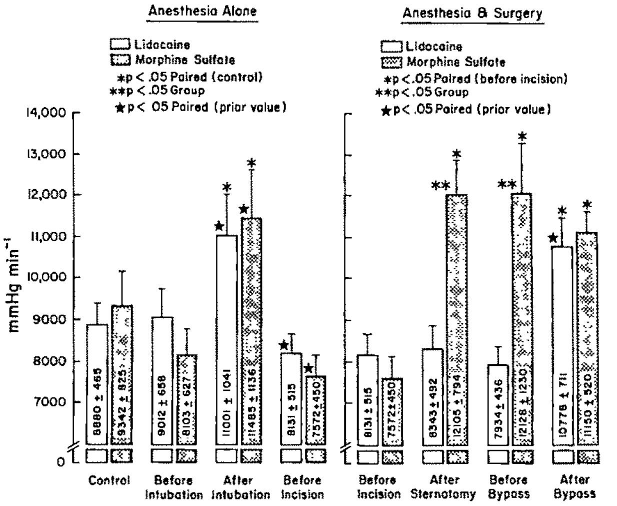


FIG 7. Rate pressure products during anesthesia, intubation, and surgery (mean ± SEM).

intubation systolic arterial blood pressure returned to control levels but decreased again prior to surgical stimulation. Cardiac index (Fig 3) decreased prior to intubation ($p < 0.05$) and remained decreased thereafter. Pulmonary capillary wedge pressures (Fig 4) did not change statistically prior to skin incision. Systemic vascular resistance (Fig 5) did not change with induction of anesthesia, but increased significantly after tracheal intubation and prior to incision ($p < 0.05$). Left ventricular stroke work index (Fig 6) decreased with induction of anesthesia ($p < 0.05$), but unlike group 1 did not change thereafter. Rate pressure product (Fig 7), increased ($p < 0.05$) following tracheal intubation while the endocardial viability ratio decreased ($p < 0.05$). These indices of the relationship

**TABLE 1**

**Endocardial Viability Ratios before Induction of Anesthesia, before and after Endotracheal Intubation***

| | Control | Before intubation | After intubation | Before incision |
|---|---|---|---|---|
| Morphine sulfate | 1.2 ± 0.11 | 0.84† ± 0.11 | 0.76† ± 0.08 | 1.0‡ ± 0.11 |
| Lidocaine | 0.92 ± 0.09 | 0.83 ± 0.10 | 0.73† ± 0.08 | 0.99‡ ± 0.08 |

* Values are means ± SEM.
† $p < 0.05$ paired with (control).
‡ $p < 0.05$ paired (prior value).

**TABLE 2**

**Endocardial Viability Ratios before Induction of Anesthesia, before and during Surgery***

| | Before incision | After sternotomy | Before bypass | After bypass |
|---|---|---|---|---|
| Morphine sulfate | 1.0 ± 0.11 | 0.93 ± 0.09 | 0.79† ± 0.09 | 0.97‡ ± 0.09 |
| Lidocaine | 0.99 ± 0.08 | 1.0 ± 0.13 | 0.91 ± 0.06 | 0.96 ± 0.07 |

* Values are means ± SEM.
† $p < 0.05$ paired with (before incision).
‡ $p < 0.05$ paired (prior value).

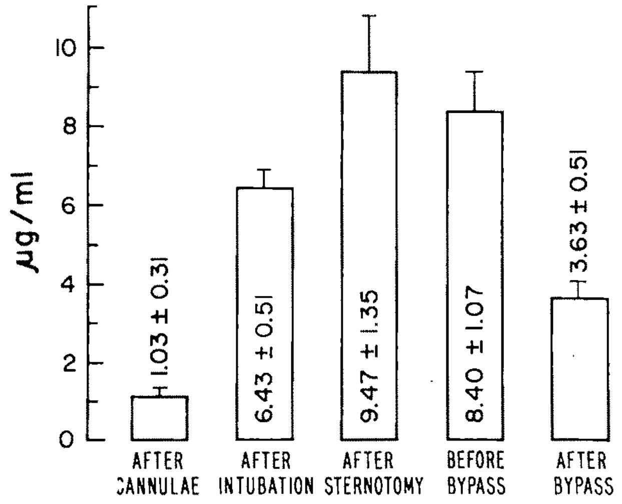


FIG 8. Lidocaine blood levels (mean ± SEM).

of myocardial oxygen supply and demand (rate pressure product and endocardial viability ratio) returned to awake control values prior to skin incision. Similar changes in these indices were observed in group 1.

## Anesthesia and Surgery

During this period the effects of surgery on cardiovascular function were examined by comparing hemodynamic data prior to skin incision with those following skin incision.

In group 1 (morphine), heart rates (Fig 1) increased from 68 to 79 beats/min ($p < 0.05$) following sternotomy and continued to increase until the start of cardiopulmonary bypass. Heart rates remained elevated following termination of bypass. Systolic arterial blood pressures (Fig 2) similarly increased during surgery from 111 to 153 torr following sternotomy ($p < 0.01$). Because of an unacceptable (>20%) increase in systolic arterial blood pressure, a few patients required vasodilators immediately prior to cardiopulmonary bypass. Cardiac index (Fig 3) decreased to preinduction levels and remained decreased throughout surgery. There were, however, no changes in the pulmonary capillary wedge pressures (Fig 4). Systemic vascular resistance (Fig 5) increased and remained elevated until bypass. Left ventricular stroke work index (Fig 6) initially increased but had decreased by the time cardiopulmonary bypass was started.

Rate pressure product (Fig 7) increased following sternotomy ($p < 0.01$) and remained elevated up to and following cardiopulmonary bypass. Similarly, the endocardial viability ratios decreased during surgical stimulation significantly below awake levels ($p < 0.05$) (Table 2). Both rate pressure product and endocardial viability ratios returned toward control levels following completion of cardiopulmonary bypass.

In group 2 (lidocaine), blood lidocaine levels (Fig 8) reached their highest values (9.47 ± 1.35 μg/ml) following sternotomy and decreased slightly prior to bypass. The infusion of lidocaine was stopped at the onset of bypass, and by the end of bypass lidocaine plasma levels had decreased even further to 3.63 ± 0.51 μg/ml. Plasma levels of lidocaine prior to cardiopulmonary bypass correlated significantly with the levels in the atrial appendage ($r = .76$, $p < 0.01$). Surgical stimulation did not increase heart rates (Fig 1) or arterial systolic blood pressures (Fig 2) in this group of patients as it did in patients given morphine ($p < 0.01$). Cardiac index (Fig 3) did not change in patients in group 2 from preincision levels prior to going on bypass. Pulmonary capillary wedge pressure (Fig 4) and systemic vascular resistance (Fig 5) both increased following sternotomy, but returned to preincision values before cardiopulmonary bypass was instituted. Left ventricular stroke work index (Fig 6) remained at preincision levels, which significantly differed from left ventricular stroke work index levels observed in patients given morphine after sternotomy ($p < 0.05$).

The rate pressure products (Fig 7) and endocardial viability ratios (Table 2) did not change statistically during surgical stimulation. The stability of these parameters stands in contrast to the changes that occurred during surgery in patients given morphine.

## Electrocardiographic and Electroencephalographic Responses

There was no electroencephalographic (EEG) evidence of seizure activity in either group. The EEG change most often encountered consisted of the emergence of slow-wave activity with the onset of anesthesia which persisted throughout the operative period. The incidence of myocardial ischemia as evidenced by the frequency of ST and T changes on the electrocardiograph was the same in both groups and was not consistently related to changes in endocardial viability ratios or rate pressure products.

## Outcome

There was no difference in morbidity or mortality between the two groups. There were two deaths secondary to myocardial failure and two myocardial infarctions with both patients surviving. These complications were divided equally between the two groups and neither complication was thought to be a result of the anesthetic.

The only difference in the postoperative courses of the two groups of patients was that patients given lidocaine could be extubated a few hours following surgery whereas most of the patients given morphine required tracheal intubation overnight.

## Discussion

In considering these data we will first examine the rationale for the doses of lidocaine and morphine used in this study and the effects of diazepam, nitrous oxide, and pancuronium on the action of these agents. In addition, the rationale for patient selection, and the hemodynamic differences that occurred between the two types of surgery (coronary artery bypass and aortic valve replacement) will be discussed. Finally, we will compare the two anesthetic regimens.

Although both lidocaine and morphine have analgesic properties when administered intravenously, morphine is greater in potency and efficacy.[22] The analgesic properties of these two drugs are, however, not necessarily related to their anesthetic potencies. Reduction of the MAC of volatile anesthetics has been used as an index of the anesthetic potency of intravenous agents, and lidocaine reduces the anesthetic MAC to a greater extent than its analgesic properties would suggest. In rats, the MAC of cyclopropane is decreased 40% by lidocaine blood levels of 14 μg/ml.[23] In the dog, a maximum reduction of the halothane MAC (approximately 45%) occurred at plasma lidocaine levels of 10 μg/ml.[24] Lidocaine blood levels of 3 to 6 μg/ml, not dissimilar to those found in our patients, decreased MAC 15 to 28% in patients receiving 70% nitrous oxide in oxygen and premedicated with morphine, 8 to 12 mg IM.[24] Similar measurements of the effect of morphine on anesthetic requirements in man are scant. Morphine premedication, 15 mg, decreases halothane MAC as much as 9%[25] and fluroxene MAC as much as 20%.[26] Morphine sulfate, in the rat, 2 mg/kg IV (the dose used in the present study), decreases cyclopropane MAC 22%.[27] Although extrapolation of these latter findings to the "equality" of our doses of morphine and lidocaine is difficult, these data do suggest that the doses of morphine and lidocaine that we used may have been equally potent in reducing anesthetic MAC.

In addition, the morphine dosage used in this study, 1 to 2 mg/kg, has been recommended for cardiac surgery when used in combination with other agents such as diazepam and nitrous oxide.[28, 29] The lidocaine dosage we used during induction of anesthesia (6 mg/kg) was given initially to attain a blood level of approximately 6 μg/ml based on previous work, corresponding to an anticipated reduction of MAC of 15 to 28%.[24] Additional lidocaine (up to 15 mg/kg) was given to increase plasma levels to approximately 10 μg/ml where, in animals, the dose response curve for reduction of MAC plateaus.[24] A major rationale for selecting the doses of lidocaine and morphine used in this study was that these doses have been used previously in the patient population being studied. While no statement equating the anesthetic potency of these agents can be made, the similarity of the hemodynamic responses prior to the onset of surgery during tracheal intubation suggests that the doses employed were equally efficacious.

Diazepam-nitrous oxide anesthesia has been reported to produce small decreases in systemic vascular resistance, without signs of cardiovascular depression.[c, d] Our observations following the addition of lidocaine as an adjunct to diazepam-nitrous oxide anesthesia during laryngeal manipulation extend and confirm earlier reports that intravenous lidocaine attenuates the hypertension and tachycardia associated with laryngoscopy when used in combination with diazepam and nitrous oxide. The increase in systolic arterial blood pressure and heart rate with tracheal intubation which occurred in patients receiving high-dose lidocaine is in agreement with the previously published data of Falk et al.[b] Similarly, we observed a decrease in cardiac index, systolic arterial blood pressure, and left ventricular stroke work index in patients given lidocaine following induction of anesthesia similar to that observed by Falk et al,[b] who studied a group of patients during induction using similar doses of diazepam and lidocaine and the same concentration of nitrous oxide. In our study, pancuronium bromide was used instead of succinylcholine to facilitate tracheal intubation. This resulted in a small, but significant, increase in heart rate (10 beats/min) prior to tracheal intubation. This was, however, the only difference between these hemodynamic data and those observed in the study by Falk et al.[b] Similarly an increase in heart rate was observed in patients given morphine following use of pancuronium bromide. In our patients, morphine sulfate when added

---

[c] Prakash R, Thrier R, Vargas A, Diaz PM: Cardiovascular effects of diazepam induction in patients for aortocoronary saphenous vein bypass surgery (abstract), presented to the American Society of Anesthesiologists, October 12, 1976.

[d] Dhadphale PB, Behrendt DM, Jackson PF, Jochim KE: The effect of diazepam on contractility in the intact human heart (abstract), presented to the American Society of Anesthesiologists October 18, 1977.

to diazepam-nitrous oxide anesthesia attenuated the expected increases in heart rate and systolic arterial blood pressure with tracheal intubation as did lidocaine, but morphine was less effective in attenuating these responses following surgical stimulation.

A frequent technique for cardiac anesthesia has as its base diazepam-nitrous oxide with a muscle relaxant, and additional adjuvant agents. Our study compares two of the different adjuvant agents, one of which (morphine) is frequently used in anesthesia. Thus, while the hemodynamic response observed in this study cannot be attributed solely to the pharmacologic properties of the adjuvant agents, it is appropriate to compare an anesthetic regimen that includes morphine to an anesthetic regimen that includes lidocaine.

When patients undergoing aortic valve replacement were compared with those undergoing coronary artery bypass (but receiving the same anesthetic regimen) we found no significant differences (other than control heart rate) in hemodynamic responses, magnitude of the responses to anesthesia or surgery. Initially, patients with aortic valvular disease had higher control heart rates, probably because they were not given propranolol preoperatively. These two types of heart disease were selected because they represent groups of patients in whom the myocardium is susceptible to ischemia resulting from imbalances in oxygen supply and oxygen demand.

The effects of the two anesthetic regimens on the relationship between the myocardial oxygen supply and demand can be demonstrated by changes in the rate pressure product and the endocardial viability ratio. These indices were altered to a similar extent in both groups during tracheal intubation. During surgical stimulation, however, the relationship between these two indices of oxygen supply and demand remained unchanged in patients given lidocaine compared to control values whereas in patients given morphine increased oxygen demand and decreased supply were suggested following surgical stimulation.

The major determinants of increased myocardial oxygen demand include increased contractility, heart rate, and myocardial wall tension. An increase in heart rate increases myocardial oxygen requirements; heart rate increased dramatically in our patients who were given morphine, but remained unchanged in those given lidocaine. So, too, an increase in contractility increases myocardial oxygen demand. Contractility is difficult to measure directly. Nonetheless, changes in left ventricular stroke work index reflect changes in contractility providing that filling pressure, as estimated by pulmonary capillary wedge pressure in this study, remains unaltered. With morphine left ventricular stroke work index increased in our patients while the pulmonary capillary wedge pressure remained constant, thus, indicating augmented contractility. With lidocaine, on the other hand, left ventricular stroke work index remained unchanged while the pulmonary capillary wedge pressure increased slightly, thus suggesting depression of contractility.

Left ventricular stroke work index, a pressure-volume product (stroke volume index times the mean arterial-pulmonary wedge pressure difference), may reflect myocardial wall tension. With morphine left ventricular stroke work index increased in our patients primarily as a result of an increase in mean arterial pressure. Stroke volume index decreased (cardiac index remained unchanged while heart rate increased); therefore, the increase in left ventricular stroke work index was due to an increase in external work (pressure work) rather than an increase in internal work (volume work). With lidocaine left ventricular stroke work index, as well as heart rate, mean arterial pressure, and cardiac index remained unchanged, thus suggesting that there was no increase in either myocardial wall tension or in its primary determinants, pressure and volume. These results are summarized in Fig. 9.

Thus, the major determinants of increased demand for oxygen by the myocardium (increased heart rate, increased contractility, and increased wall tension) all increased with sternotomy in our patients who were given morphine. An increase in external work, which is associated with a greater oxygen demand than is an increase in internal work, was the major factor in increasing wall tension in these patients. Patients given lidocaine on the other hand, did not demonstrate increases in oxygen demand as reflected by these determinants (heart rate, contractility, and wall tension did not increase).

The ability of lidocaine to diminish the hyperten-

| | Induction | | Intubation | | Surgical Stimulation | |
|---|---|---|---|---|---|---|
| | Lidocaine | Morphine | Lidocaine | Morphine | Lidocaine | Morphine |
| Heart Rate | ↑ | ↑ | ↑ | ↑ | ↑ → | ↑ |
| Blood Pressure | ↓ | ↓↓ | ↑ | ↑ | → | ↑↑ |
| Cardiac Index | ↓ | ↑ | → | ↑ | ↓ → | → |
| SVR | ↑ | ↓↓ | ↑ | ? | ↑ | ↑ |
| PCW | sl ↑ → | sl ↓ → | sl ↓ → | sl ↑ → | sl ↑ | → |
| PRP | → | → | ↑ | ↑ | → | ↑↑ |
| LVSWI | ↓ | ↓ | → | ↑ | ↓ → | ↑↑ |

FIG 9. Summary of hemodynamic measurements. (↑ signifies an increase, ↓ a decrease, and → no change, "sl" refers to slight changes).

sive-tachycardiac response to noxious stimuli was more apparent during surgical stimulation than tracheal intubation. This observation probably reflects the fact that higher blood levels of lidocaine were present during surgery. Lidocaine's efficacy in abolishing the autonomic response to surgical stimulation appeared greater than that of morphine, a difference not observed during tracheal intubation. The apparent ability of morphine to ameliorate the response to tracheal intubation may partly reflect conditions prior to this stimulus, namely a lower systolic arterial blood pressure secondary to a reduced systemic vascular resistance in the morphine-treated group prior to tracheal instrumentation. Thus, a greater increase in systolic arterial blood pressure resulting from tracheal intubation of these patients (29 torr vs 12 torr in the lidocaine group) resulted in a postintubation systolic arterial blood pressure not differing from those measured in the lidocaine group. On the other hand, by the time of the skin incision, systemic vascular resistance was identical in both groups. Following sternotomy, there was a significantly greater increase in systolic arterial blood pressure (and a higher final systolic pressure) in patients receiving morphine.

Myocardial depression has been reported when nitrous oxide is added to morphine anesthesia.[30-32] Since the pulmonary capillary wedge pressure did not change and cardiac output increased after induction of anesthesia but prior to tracheal intubation, it is difficult to attribute the hemodynamic effects of morphine-nitrous oxide anesthesia that we observed to direct myocardial depression.

The beneficial effects of lidocaine may best be explained on the basis of direct myocardial depression. Although small decreases in the systemic vascular resistance have been reported with intravenously administered lidocaine,[17] these decreases were not observed under the conditions of this study. The decreases in cardiac index, systolic arterial blood pressure, and left ventricular stroke work index, and the increase in pulmonary capillary wedge pressure were compatible with direct myocardial depression. The effect of high dose intravenously administered lidocaine on the autonomic nervous system is unknown, and depression of responses to tracheal intubation and surgical stimulation secondary to depression of the autonomic nervous system cannot be excluded. It is interesting to note, however, that systemic vascular resistance was above awake levels after tracheal intubation and sternotomy, suggesting some peripheral autonomic activity causing reflex vasocontriction in response to stimulation.

It is concluded that lidocaine can safely be used as an intravenous anesthetic agent in cardiac surgical patients, although it must be used cautiously in patients with compromised cardiac function. Lidocaine produces a controlled dose-related depression in myocardial performance which can be used to inhibit reflex increases in blood pressure and pulse rate during tracheal intubation and during surgical stimulation. Lidocaine, thereby, favorably influences myocardial oxygen requirements. Whereas this depression does not inhibit these reflexes, which adversely affect myocardial oxygen supply and demand during tracheal intubation, any more than morphine, lidocaine was superior to morphine in depressing these responses during the period of surgical stimulation.

## REFERENCES

1. King BD, Harris LC Jr, Griefenstein FE, et al: Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 12:556-566, 1951
2. King BD, Elder JD, Proctor DF, et al: Reflex circulatory responses to tracheal intubation performed under topical anesthesia. Anesthesiology 15:231-238, 1954
3. Wycoff CC: Endotracheal intubation: effects on blood pressure and pulse rate. Anesthesiology 21:153-158, 1960
4. DeVault M, Griefenstein FE, Harris LC Jr: Circulatory responses to endotracheal intubation in light general anesthesia—the effect of atropine and phentolamine. Anesthesiology 21: 360-362, 1960
5. Forbes AM, Dally FG: Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. Br J Anaesth 42:618-624, 1970
6. Strong MS, Vaughan CW, Mahler DL, et al: Cardiac complications of microsurgery of the larynx: etiology, incidence and prevention. Laryngoscope 84:908-920, 1974
7. Burstein CL, LoPinto FJ, Newman W: Electrocardiographic studies during endotracheal intubation. I. Effects during usual routine techniques. Anesthesiology 11:224-237, 1950
8. Converse JG, Landmesser CM, Harmel MH: Electrocardiographic changes during extubation: a study of electrocardiographic patterns during endotracheal anesthesia including those seen during intubation, endotracheal suction, and particularly extubation. Anesthesiology 13:163-168, 1952
9. Burstein CL, Woloshin G, Newman W: Electrocardiographic studies during endotracheal intubation. II. Effects during general anesthesia and intravenous procaine. Anesthesiology 11: 299-312, 1950
10. Katz RL, Bigger JT Jr: Cardiac arrhythmias during anesthesia and operation. Anesthesiology 33:193-213, 1970
11. Schaub RG, Lenole GM, Pinder GC, et al: Effects of lidocaine and epinephrine on myocardial preservation following cardiopulmonary bypass in the dog. J Thorac Cardiovasc Surg 74: 571-576, 1977
12. Stoelting RK: Circulatory response to laryngoscopy and tracheal intubation with or without prior oropharyngeal viscous lidocaine. Anesth Analg 56:618-621, 1977
13. Stoelting RK: Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 47:381-384, 1977
14. Denlinger JK, Ellison N, Ominsky AJ: Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. Anesthesiology 41:409-412, 1974

15. Steinhaus JE, Howland DE: Intravenously administered lidocaine as a supplement to nitrous oxide-thiobarbiturate anesthesia. Anesth Analg 37:40-46, 1958
16. Steinhaus JE, Gaskin L: A study of intravenous lidocaine as a suppressant of cough reflex. Anesthesiology 24:285-290, 1963
17. Boudoulas H, Schaal SF, Lewis RP, et al: Negative inotropic effect of lidocaine in patients with coronary artery disease and normal subjects. Chest 71:170-175, 1977
18. Hoffman JIE, Buckberg GD: Regional myocardial ischemia—causes, prediction, and prevention. Vasc Surg 8:115-130, 1978
19. Hoffman JIE, Buckberg GD: Pathophysiology of subendocardial ischemia. Br Med J 1:76-79, 1975
20. Hoffman JIE, Buckberg GD: The myocardial supply:demand ratio—a critical review. Am J Cardiol 41:327-332, 1978
21. Keenaghan JB: The determination of lidocaine and prilocaine in whole blood by gas chromatography. Anesthesiology 29: 110-112, 1968
22. Moore PA, Burney RG: Analgesic properties of lidocaine in mice. Anesth Analg 58:85-87, 1979
23. DiFazio CA, Niederlehner JR, Burney RG: The anesthetic potency of lidocaine in the rat. Anesth Analg 55:818-821, 1976
24. Himes RS Jr, DiFazio CA, Burney RG: Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology 47:437-440, 1977
25. Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 25:302-306, 1964
26. Munson ES, Saidman LJ, Eger EI II: Effect of nitrous oxide and morphine on the minimum anesthetic concentrations of fluroxene. Anesthesiology 26:134-139, 1965
27. Hoffman JC, Difazio CA: The anesthetic sparing effect of pentazocine, meperidine and morphine. Arch Int Pharmacodyn Ther 186:261-268, 1970
28. Kaplan JA: Cardiac Anesthesia. New York, Grune & Stratton, 1979, pp 3-508
29. Lowenstein E: Morphine "anesthesia"—a perspective. Anesthesiology 35:563-565, 1971
30. McDermott RW, Stanley TH: The cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 41:89-91, 1974
31. Lappas DG, Buckley MJ, Laver MB, et al: Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary artery-surgery. Anesthesiology 43:61-69, 1975
32. Eisele JH, Reitan JA, Massumi RA, et al: Myocardial performance and nitrous oxide analgesia in coronary artery disease. Anesthesiology 44:16-20, 1976

---

## Warning Arrhythmias before Ventricular Tachycardia

In order to determine the relationship of paroxysmal ventricular tachycardia (PVT) to any antecedent (premonitary) ventricular arrhythmias during the early phases of acute myocardial infarction, 24-hour Holter monitoring was begun on 52 male patients an average of 12.6 hours after the onset of prolonged chest pain that was subsequently documented as acute infarction. Twenty-four patients had PVT and 28 did not. PVT was defined as three or more consecutive beats of ventricular origin at a rate greater than 120 beats per minute. The frequency of premature ventricular complexes (PVCs), "the prematurity index," and incidence of pairing during the 10 minutes immediately preceding PVT were obtained from continuous 10-minute rhythm strips. There was no positive correlation between PVT and the number or complexity of PVCs in the 10 minutes immediately before ventricular tachycardia. These findings suggest that there is no consistent pattern or frequency of ventricular arrhythmia that could be identified as premonitory for PVT during the immediate pre-PVT period, even during the acute phase of myocardial infarction in man. (*De Soyza N, Meacham D, Murphy ML, et al: Evaluation of warning arrhythmias before paroxysmal ventricular tachycardia during acute myocardial infarction in man. Circulation 60:814-818, 1979*)

# SPECIAL article

# The History of Drug Inhalation: A Brief Overview

J. S. Gravenstein, MD*

GENERAL anesthesia could not be accepted by the medical profession until three concepts had reached maturity. These concepts are, first and most obvious, a predictably reversible state of unconsciousness can be safely produced. Second, this state of unconsciousness is caused by use of a single specific drug, not an elaborately compounded mixture of medicines so widely used at the time. Finally, the drug is administered by inhalation, not as in the case of most contemporary potent medicines, orally.

The history of anesthetic drugs and the concept of anesthesia have been well described.[1-6] We hear less about the history of medicinal inhalations, the topic of my treatise. Under this general heading one might include the inhalation of sea air for health reasons, fumigation for cleansing rooms of evil influences, and the account of miasmas or caves with an atmosphere injurious to the health of man and beast. These I shall not discuss.

Two old but distant relatives of inhalation anesthesia I shall mention only briefly. One is the voluntary breath holding, or hyperventilation, which—according to Ellis[5]—was practiced for its effect on the psyche. The other is the often mentioned Greek oracle at Delphi where a priestess, Pythia, placed herself into a trance by chewing laurel leaves and breathing emanations from the earth. The two examples deserve notice because both give evidence that long before the Christian era people were aware that under special circumstances breathing could have uncommon effects on the mind.

In the following pages, I shall sharpen the focus and discuss examples closer to general inhalation anesthesia, i.e., occasions where man purposefully altered the composition of the ambient air for a local or general effect often but not invariably with therapeutic intent. Much of the material here has been taken from historical texts.[1-6] To these well described stories I shall not give bibliographic references. Material from lesser known sources, however, is documented. The purpose is to review the background and history of medicinal inhalation which eventually led to and culminated in inhalation anesthesia.

Vapors, fumes, or gases can be either self-administered or they can be administered by others. They can be given without instruments or with elaborate machines. The Figure shows a suggested classification. The most sophisticated clinical inhalations, e.g., modern anesthesia, are represented in the right lower corner of the Figure. The simplest and probably oldest use of inhalations, communal smoking without pipes, is shown in the left upper corner. Two important conceptual advances separate these extremes. One is the appearance of a person, eventually the anesthesiologist, who administers the artificial airs without partaking in their inhalation. The other is the development of equipment and machines for the accurate administration of the artificial airs. As we shall see, the evolution from simple to sophisticated did not progress in step with the march of time.

---

* Graduate Research Professor.

Received from the Department of Anesthesiology, University of Florida College of Medicine, Box J254 JHMHC, Gainesville, Florida 32610. Accepted for publication September 21, 1979.

| SIMPLE | | WHO administers the drug? | | | |
|---|---|---|---|---|---|
| | | It is self-administered | | It is administered by a person | |
| HOW is the drug administered | without a mechanical device | by a group | by an individual | to a group | to an individual |
| | with a mechanical device | by a group | by an individual | to a group | to an individual |

COMPLEX

FIGURE. Organization of the features of drug inhalation ranging from the simplest (self-administered without a mechanical device by a group, e.g., communal smoke inhalation around an open fire) to the most complex (drug administered by a person to an individual using a mechanical device, e.g., current anesthesia practice).

## Self-Administration

### By a Group without a Mechanical Device

Perhaps the voluntary inhalation of smoke started with the accidental discovery that smoke produced when certain plants were burned had desirable effects. This occurred at different times in different cultures but must have been common before recorded history. A relatively late account of one example is given by Herodotus, the Greek historian who lived around 450 BC. He mentioned the Massagetai, a nomadic people of central Asia north of the Oxus River, and wrote that they had discovered trees that yielded a special fruit. The tribe would assemble around the fire and smell the fruit as it burned. From its scent they became intoxicated and when they threw more fruit into the fire, the Massagetai began to rise and sing and dance.

For more than 2500 years, incense has been burned in religious ceremonies and other settings. One of the oldest and best known representations of a censer is found on the breast of the Sphinx of Giza, which dates to about 1530 BC. In these censers a great variety of aromatic substances, vegetable and animal, were used. While the purpose of incense burning may have been ritual, for the sake of importing a sweet smell to the air, for sanitary fumigation, or to provide in its rising smoke a vehicle for the ephemeral to ascend to the heavens, Plutarch attributed to its sweet odor a "benign physiological effect."[7] The censer came in many different shapes but most were essentially pots with perforated lids that allowed the smoke to escape. In a well known story from *A Thousand and One Nights* the soporific fumes were dispensed from a censer to put to sleep the guards of a camp.

### By an Individual without a Mechanical Device

At times, the communal inhalations may have had religious purposes, or they may have served social needs. In either case, smoke inhalations were not practiced to cure a specific disease or influence a particular symptom. However, somewhere the transition was made and purposeful inhalations by a single person for therapeutic reasons were introduced. This was a significant advance. Examples of such individual inhalations without instruments abound. One of the oldest examples, drawn from mythology, is the story of Aphrodite, the Greek goddess of seafaring and love. As such she knew several men, among them the handsome Adonis. When Aphrodite learned that he had been killed during a boar hunt, she threw herself upon a bed of lettuce to assuage her grief. To the people of ancient times, this response to grief was in no way odd and required no further explanation. Lettuce as a pharmakon, is mentioned repeatedly and was no stranger than crocodile skin, although obtained perhaps more readily and hence used more frequently. The point is that Aphrodite threw herself onto the lettuce to inhale its therapeutic emanations. That a gentle scent from certain plants was believed capable of producing hypnotic effects is born out by many later statements. Thus, Dioscorides (a Greek physician who lived in the 1st century AD and who wrote authoritatively on *materia medica*) mentioned apples that "are narcotic when smelled too." Celsus (the "Cicero of Medicine" in the 1st century AD) described placing mandrake apples under the pillow as a useful hypnotic. The idea of incorporating the hypnotic into the pillow was not forgotten. In 1787 the physician attending George III sought relief for the insomnia from which the king suffered. He prescribed a pillow filled with hops.

One might argue that such a pillow was thought to act by contact rather than by its scent, just as placing a textbook under the pillow is said to facilitate the assimilation of its content into the head of the sleeper who rests on it (perhaps). A curious German prescription from 1733[8] promises benefit by permeation as well as inhalation or olfaction: For treatment of a head cold and "as a tonic for the head fix yourself a little bag with sweet marjoram, wild thyme, garden thyme, laurel and black caraway and place it upon your head; you can also—with great advantage—smell of it frequently because these herbs serve to strengthen you and reduce the cold."

Another method for self-administration called for incorporation of the active substance in a candle. For toothache, Dr. Andrew Borde, a colorful physician from Sussex who at one time attended Henry VIII, prescribed in the 16th century "a candell of waxe with henbane seeds which must be lighted so that the perfume of the candell do enter into the tooth." Later a German text[8] recommended for toothache the smoke of burning hemp seeds, sweet marjoram, and sugar. While the intent in both instances was to provide a local effect, inhalation could not have been avoided.

At about the same time, i.e., in the 18th century, ether inhalations were prescribed primarily for lung disease. The drug was placed into a cup. Sometimes a candle under the cup helped evaporation of what was probably a mixture of diethyl ether, alcohol, and ethereal oils. Today glue sniffers and smokers of cigarettes containing tobacco, bronchodilating drugs, or marihuana fit into the category of inhalation by single individuals using no mechanical device.

## By a Group with a Mechanical Device

In developing and refining inhalation of fumes or smoke, it became necessary to invent techniques to gather and deliver the inhaled substance in a more convenient and manageable way than was possible using an open fire. An example of this cited by Herodotus refers to the early discovery of what we today might call a semi-open method. The semi-open method of inhalation of drugs has fallen out of vogue and it may be necessary to remind the reader that in anesthesia practice a few decades ago the term was used to describe the administration of open drop anesthesia—usually with ether. Instead of keeping the system quite open, i.e., only a gauze-covered mask onto which the drug was dripped, a towel was wrapped around the patient's face and mask so that a chimney was formed with a wide opening on top into which the ether was dripped. A forerunner to that method was used by the Scythians, a people living to the north of the Black Sea. They also contained the fumes by wrapping something around their "vaporizer." Herodotus related: "When they have set up three pieces of wood leaning against each other, they extend round them woolen cloths; and having joined them together as closely as possible, they throw red-hot stones into a vessel placed in the middle of the pieces of wood and the cloths . . . When (they) have taken some seed of . . . hemp, they creep under the cloths, and then put the seed on the red-hot stones. The Scythians, transported with the vapor, shout aloud" (quoted by Ellis[5]).

## By an Individual with a Mechanical Device

It requires only a small conceptual step to take a censer, insert a reed into the hole of its perforated lid, and inhale the smoke for medicinal purposes. Indeed, such smoke pots were used in ancient Egypt, Greece, and Rome, even into the 18th century of our time.[9] These devices had only one hole in the lid, the better to capture the smoke of hemp, poppies, and other aromatic herbs that were burned. Because the rising smoke was hot, it was necessary to inhale with an open mouth. Hippocrates advised use of a wet sponge to cool lips and face. Galen, the Greek physician who practiced in Rome about 150 AD, described a refinement and thereby introduced the disposable mouth piece. He said (quoted by Waldenburg[9]): "The end of the reed is very hot. Take an empty egg with holes on either end into your mouth and insert the reed through it."

A much later modification of this venerable method was recommended in 1733 by Seelig[8] who wrote, "take a new pot, put one hole into its bottom and another into its belly. Through this side hole introduce a red-hot poker which you bring into contact with wax containing medicinal herbs." He did not mention that the pot had to be turned upside down to work. That must be understood as he concluded by saying: "Now you can guide the smoke nicely and tightly bundled into your mouth." This 18th century remedy for toothache combines the medicated "candell" of Borde and the pot of Hippocrates.

The Persian water pipe—from which opium and hemp could be and was smoked—and medicated tobaccos for pipes, are all relatives of this smoke-pot category. The profusion of today's drug culture accouterments are direct descendants of these devices.

One curious device that facilitated aspiration into the nose—not of smoke but of powders—was described by Humboldt (quoted by Ellis[5]) who observed that the South American Ottomac Indians inserted a Y-shaped hollow bird bone into their nostrils to sniff and inhale the powder made of mimosacea. Nasal prongs and mouth pieces had been thought of long before modern inhalation therapists reinvented them.

The small improvised ether inhalers used in the early years of the 19th century are well known. A funnel was placed upside down over a cup containing ether. A quill was wedged between funnel and cup to lift the funnel brim a little and admit more or less air to dilute the ether vapor. The patient then inhaled carefully by holding the funnel tip with the lips. No empty egg was needed!

In European folk medicine, steam inhalations and breathing of aromatic vapors were widely practiced well before and long after the introduction of inhalation anesthesia. Inhalations were recommended in popular medical treatises and devices for such inhalations were described in the current literature.[9-13]

## Administered by Others

Now we are ready for the giant step, the introduction of the anesthetist. The Bible reports (Genesis 2: 21) that God "caused a deep sleep to fall upon Adam" when He took one of Adam's ribs. Some take this as evidence for a divine mold for the anesthesiologist. A more modest view might be in order as some forerunners to anesthesiologists do not invite emulation.

### To a Group without a Mechanical Device

This category does not provide many examples. The only one I could fit (with a little strain) into this slot comes from Holland, France, and England of the mid 1800s.[13] At times of pertussis epidemics, many children needed treatment. There was a belief that they were helped by breathing the air in certain rooms of illuminating gas works. The children were taken there and allowed to breathe the "Gasluft" for "some time," reputedly with excellent results. Two to three visits were usually necessary for a cure.

### To an Individual without a Mechanical Device

A grim example is provided by the history of witch burnings. It was apparently customary to cut short the suffering of the condemned by stifling them with smoke before the flames reached them. Also in the realm of the macabre is another application of the charming "candell" as conceived by Edgar Allen Poe[15]; ". . . in reading some French memoirs, I found an account of a nearly fatal illness that occurred . . . through the agency of a candle accidentally poisoned. This idea struck my fancy at once . . . I substituted, in his bedroom candle stand, a wax light of my own making for the one which I there found. The next morning he was discovered dead in his bed, and the coroner's verdict was - 'death by the Visitation of God'."

Friendly applications, however, were plentiful. These can be divided into two categories, the medicated smoke and the drugged sponge. The former is already familiar and comprises innumerable references to the preparation of medicinal smokes at the bedside. While these go far back into antiquity, a relatively recent application dates from 1809 when a physician placed opium on a red-hot iron next to the patient's bed in cases of hysteria, depression, or fits.[9]

Now we turn to the sponge. Because it is not an instrument or a contrived machine, I list it here. It seems to have been favored more because it served as a flexible vessel than anything else. Thus it was used to bring close to the patient's nostrils soporific medicines, for instance one containing opium, hyoscyamus, and the juice of unripe mulberry, all according to the monk physician Theodoric, who lived about 1490. His "oleum lateribus" was thought powerful enough to produce surgical anesthesia. Indeed, the soaked sponge could be dried in the sun and then, whenever needed, activated by adding water.

Undoubtedly the best known reference to the sponge occurs in the Bible. In the account of the Crucifixion, we are told by John (The Gospel According to St John: Chap 19, verse 29): "Now there was set a vessel full of vinegar; and they filled a sponge with vinegar and put it upon Hyssop and put it to His mouth." It is not certain that it was really vinegar or a sour wine—perhaps drugged—that was offered to Christ who thirsted. Nor do we know with certainty the purpose of offering vinegar or wine at crucifixion. Both vinegar and sponges recur in many medicinal settings. Through the centuries, vinegar was employed to revive the faint by its pungent smell.[8] Others used effervescent spirits placed before nose and mouth for the same purpose.[15] This is still practiced today but has obviously been well established for many centuries.

### To a Group with a Mechanical Device

Asian thieves produced soporific smoke in pots and blew the smoke into the houses of people they were planning to rob. One detailed description (quoted by

Waldenburg[9]) relates to an Englishman traveling in China. One night he found himself overcome by opium smoke in his bedroom. The smoke was being blown by thieves into his room through a crack in the ceiling. As soon as the Englishman was too sleepy to respond, the thieves enlarged the hole in the ceiling, climbed into the room and stole his money. This account antedates the introduction of anesthesia by many decades. Thieves have now adopted the use of better drugs and occasional stories from the United States and Europe report that thieves still attempt to anesthetize their victims.

Recently this method was employed in campsites of Southwestern Europe where thieves blew anesthetics into the tents of their victims. Anesthesiologists may wonder about these reports. It is not easy to reach stupefying concentrations in a room or tent. Perhaps the thieves, emboldened by confidence in their pharmacologic stealth and aided by a placebo effect, were particularly swift while their victims slumbered no more deeply than usually.

### To an Individual with a Mechanical Device

Historic inhalers for oxygen, nitrous oxide and ether, and gas masks have been well described in the literature and I shall not discuss them here. As soon as a specific agent, and the need to administer it by the inhalation route, and the decision to confine it were clearly formulated, various devices for the administration of anesthetics were invented. Indeed, anesthesia apparatus was a striking feature of the earliest anesthetics given by William Morton and John Snow. Both took pains to have the anesthetic vapor concentrated and thus limited to the patient; both built vaporizers related in concept to the smoke pots of the ancients. Both had access to the literature describing inhalation devices with tubes and valves and mouth pieces or gas masks. In his inhaler, Morton even incorporated a sponge, that most venerable instrument of anesthesia lore. The other pioneer, Crawford W. Long, was apparently more influenced by the conceptually simpler application of ether in the "ether frolics," where users without instruments vaporized ether for self-administration. Long vaporized ether on a cloth. For almost 100 years the majority of anesthetics in the world were given by open drop rather than with the help of a vaporizer as designed by Morton or Snow.

Why is it that these inhalers, with such distinguished parentage and hoary history, were ignored? Duncum[16] thinks that Morton's apparatus fell into disuse because he applied for a patent. This led the Boston surgeons to employ a bell-shaped sponge which they held over the patient's nose and mouth. But then why did Snow's apparatus fail to be copied? He designed it because he considered "a knowledge of the strength of the vapour as being essential to a correct determination of the state of the patient at all times."[17] He was more than 100 years ahead of his time with this reason for seeking to determine the "proportions of air and vapour." Most other anesthetists obviously thought this unnecessary, too expensive, or too cumbersome, even though a few recommended inhalers of various designs.

Looking back over the centuries we observe that the developments of new concepts do not unfold in orderly progression, but culture, knowledge, personalities, circumstance, and need conspire to establish finally what was available for a long time, either in concept or as a brilliant, early demonstration.

## Summary

When anesthesia made its triumphant entry more than 130 years ago, it established inhalation as a major and important route for the uptake of drugs. A brief review of the colorful history of medicinal inhalations shows that man has inhaled at least as long as written records exist, not only to sustain but also to modify life.

ACKNOWLEDGMENT

Mr. Patrick Sim, Librarian, Wood Library-Museum of Anesthesiology, The American Society of Anesthesiologists, Park Ridge, Illinois, was helpful in finding several references, and the Wood Library provided an ideal setting for reading and writing.

REFERENCES

1. Foy G: Anaesthetics, Ancient and Modern. Dublin, Balliere Tindall & Cox, 1889
2. Müller B: Narkologie. Berlin, R Trenkel, 1903
3. Burroughs Wellcome and Co: Anaesthetics, Ancient and Modern: An Historical Sketch of Anaesthesia. American Medical Association, Atlantic City, 1907
4. Keys TE: The History of Surgical Anesthesia. New York, Dover, 1963
5. Ellis ES: Ancient Anodynes: Primitive Anaesthesia and Allied Conditions. London, Wm Heinemann, 1946
6. Davison MHA: The Evolution of Anaesthesia. Baltimore, Williams & Wilkins, 1965
7. Birdwood GCM: Incense, in Encyclopaedia Britannica, Chicago, Encyclopaedia Britannica Inc, 11th edition. Vol 14, 1910, pp 348–353
8. Seelig GA: Des Freiwillig Aufgesprungenen Granat-Apffels Des Christlichen Samariters Anderer Theil. Nürnberg, Johann Adam Schmidt, 1733.
9. Waldenburg L: Die Inhalation der Zerstäubten Flüssigkeiten sowie der Dämpfe und Gase in ihrer Wirkung auf Krankheiten der Atmungsorgane. Berlin, Georg Thieme, 1864.

10. C . . . L: Account of a machine for curing coughs, and other disorders of the lungs, invented by Mr A . . . r, a teacher in this town. London, Derby, Nov 15, 1748, Gentleman's Magazine and Historical Chronicle, 18:486, 1748
11. Cameron GD: Description of an apparatus for inhaling the vapor of hot water. The London Medical and Physical Journal 1:196–198, 1823
12. Smee A: On the inhalation of ammonia gas as a remedial agent. The London Medical Gazette 32:59–62, 1843
13. Lewin G: Die Inhalations—Therapie in Krankheiten der Respirationsorgane. Berlin, A Hirschwald, 1865
14. Poe EA: The imp of the perverse, in The Complete Poems and Stories. New York, Alfred Knopf, 1946
15. Wohl Geprüfte, ganz Sichere und Schleunige, auf Erfahrung Gegründete Hilf—und Rettungsmittel für Verunglückte Personen. Johann Andreas Kienreich Verlag, Gratz, 1793
16. Duncum B: The Development of Inhalation Anaesthesia. New York, Oxford University Press, 1947
17. Snow J: On the inhalation of the vapour of ether in surgical operations. London, 1847. Reproduced under the auspices of the Wood Library Museum of Anesthesiology. Philadelphia, Lea & Febiger, 1959

---

## Bacteremia from Pressure Transducers

Primary *Serratia marcescens* bacteremia developed in 17 patients in an intensive care unit after exposure to pressure monitoring devices. Presterilized individually packaged disposable transducer domes, stopcocks, and connecting lines were attached to the pressure transducer heads. A study showed that all of the transducer heads were contaminated with *S. marcescens,* and prospective culturing of 110 pressure monitoring lines disclosed a 24% rate of contamination with the same organism. Hand contamination occurs at the time the equipment is initially assembled; in five of eight trials, transmission was shown experimentally to occur by direct inoculation of open ports. Routine disinfection of the transducer heads with glutaraldehyde not only effectively decontaminated all pressure monitoring lines in use, but also controlled the outbreak. (*Donowitz LG, Marsik FJ, Hoyt JW, et al: Serratia marcescens bacteremia from contaminated pressure transducers. JAMA 242:1749–1751, 1979*)

# CLINICAL reports

## Hepatitis Associated with Enflurane Anesthesia

**Fernando V. Ona, MD,*
Henry Patanella, MD,† and
Asif Ayub, MD‡**

Adverse hepatic responses have been reported after exposure to halothane, methoxyflurane, and fluroxene.[1-3] The following case indicates that repeated exposure to enflurane (Ethrane; 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether) may also be associated with a hepatic reaction resembling hepatitis. This case supports the earlier reports of jaundice and liver damage following enflurane anesthesia.[4-7]

### Case Report

A 66-year-old woman was admitted to St. Mary's Hospital on January 22, 1979 for repair of a 3 x 3-cm scalp laceration. Past history included essential hypertension since 1957 controlled by guanethidine sulfate, 10 mg three times a day, intrinsic bronchial asthma treated with chlorpheniramine maleate, 8 mg twice a day, and uncomplicated mitral valve prolapse. In 1972, she had an appendectomy under spinal anesthesia for acute perforated appendicitis. At that time intravenous cephalothin, 8 g/day was administered for 1 week. She denied any history of hepatitis or prior exposure to anyone with viral hepatitis.

On January 23, 1979, the patient underwent debridement of the scalp laceration and excision of nonviable parietal bone. The operation was performed under enflurane anesthesia. The procedure lasted 90 minutes and was uneventful. Prophylactic antibiotics were administered in the form of cephalothin, 2 g every 6 hours intravenously for 2 days, followed by cephalexin, 500 mg every 6 hours orally for 5 days. Levels of total serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), and alkaline phosphatase were within normal limits before and 6 days after the operation. The patient had an uncomplicated postoperative clinical course until her second operation.

On January 30, 1979, split thickness skin grafts were applied to the scalp wound under enflurane anesthesia. The operation lasted 35 minutes and the patient tolerated the procedure very well; blood loss was negligible and there was no hypotension. She received one prophylactic dose of cephalothin, 3 g intravenously 5 hours postoperatively.

Approximately 12 hours after the operation, the patient developed high grade fever, chills, generalized urticarial rash, nausea, and vomiting. She became restless, confused, and developed urinary and fecal incontinence. Physical examination revealed a toxic appearing woman with temperature of 40 C rectally, blood pressure of 130/70 mm Hg, pulse rate of 120/min, and respiratory rate of 20/min. There was no evidence of wound infection in the area of the skin graft. The skin showed generalized urticarial rash and no icterus. Auscultation of the heart revealed midsystolic click and grade II short systolic murmur at the apex. The liver and spleen were not palpable and the remainder of the examination was within normal limits.

After the onset of fever, in spite of the absence of obvious wound infection, cefamandole, 2 g, was given intravenously and after two doses this was replaced by tetracycline, 250 mg three times a day orally. The tetracycline was discontinued after three doses when there was no change in her febrile course. Her fever persisted for 3 days but spontaneously subsided on the 4th postoperative day in the absence of antibiotics.

Pertinent laboratory data obtained immediately after the onset of fever revealed a normal hemoglobin and hematocrit and a white blood cell count of 13,000 with 86% polymorphonuclear cells, 12% band cells, and 2% lymphocytes. Two days later, the white blood count was 11,500 with 68% polymorphonuclear cells, 18% band cells, 3% eosinophils, 6% lymphocytes, and 5% monocytes. At the same time (2 days after the second operation) total serum bilirubin increased to 2.6 mg/100 ml (direct 1.3 mg), serum glutamic oxaloacetic transaminase (SGOT) was 84 units (normal, 8

---

* Assistant Professor of Medicine.

† Clinical Assistant Professor of Medicine.

‡ Instructor of Medicine.

Received from the Department of Medicine, University of Rochester School of Medicine, St. Mary's Hospital, 89 Genesee Street, Rochester, New York 14611. Accepted for publication October 21, 1979.

Reprint requests to Dr. Ona.

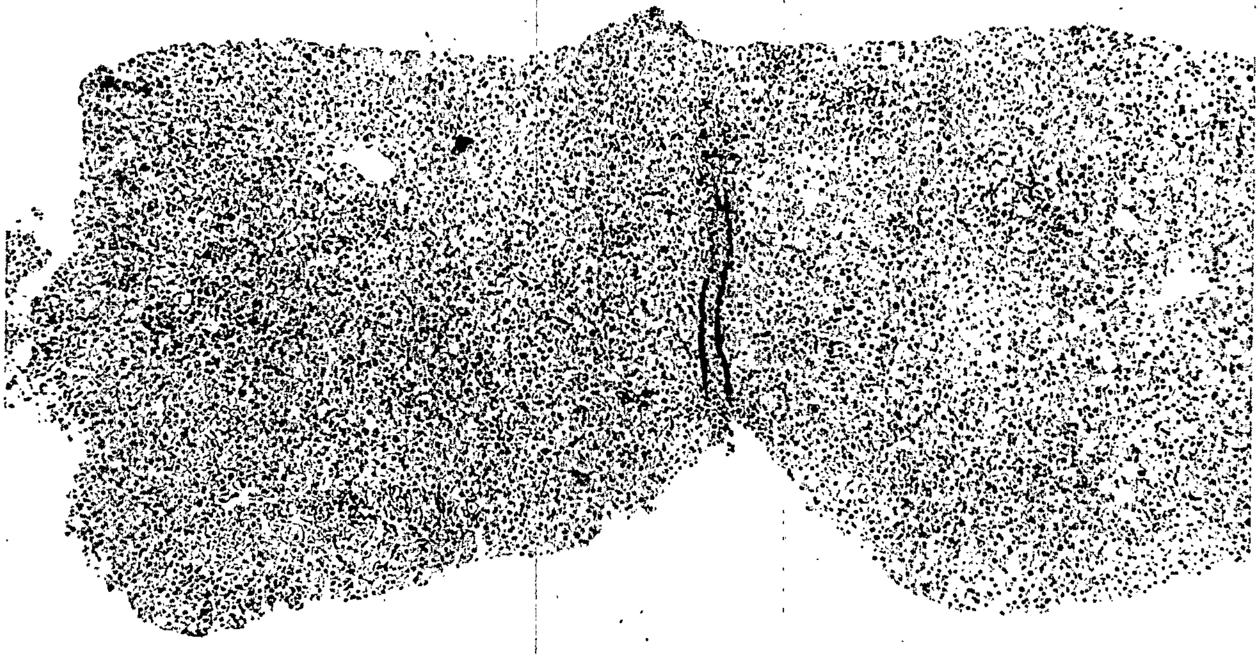


FIG 1. Needle biopsy of the liver 10 days after enflurane anesthesia, showing patchy areas of hepatocellular necrosis with increased infiltration of mostly mononuclear cells. Hematoxylin and eosin; ×16.

to 30 units), serum glutamic pyruvic transaminase (SGPT) was 73 units (normal, 5 to 35 IU), alkaline phosphatase was 215 IU (normal, 45 to 110 IU), and gamma glutamyl transpeptidase (GGTP) was 391 IU (normal, 15 to 85 IU). Prothrombin and partial thromboplastin times were normal. Multiple blood and urine cultures were negative. Tests for serum hepatitis B surface antigen ($HB_sAg$), antimitochondrial antibody, smooth muscle antibody, and antinuclear antibody were negative. Ultrasonography of the liver, gallbladder, and pancreas revealed no abnormalities.

Percutaneous liver biopsy 10 days after the second operation revealed patchy areas of hepatocellular necrosis mainly in the midzone and periphery of the lobule with predominantly mononuclear cell infiltrations (Fig 1). Acidophilic bodies were present (Fig 2) and increased number of eosinophils in the portal tract were noted (Fig 3). No viral-type inclusions were identified and the hepatocytes had no ground glass appearance to indicate $HB_sAg$ hepatitis. Liver function tests at the time of biopsy showed a total bilirubin of 0.9%, SGOT of 265 units, SGPT of 300 units, and alkaline phosphatase of 368 IU. The patient was discharged 3½ weeks after admission clinically improved but with persistently elevated SGOT of 165 units, SGPT of 300 units, and alkaline phosphatase of 291 IU. Levels of these liver enzymes gradually returned to normal 4 weeks after discharge.

## Discussion

This case of hepatitis may represent hypersensitivity to enflurane. The history of bronchial asthma and the sudden appearance of unexplained fever, generalized urticarial rash, nausea and vomiting within 12 hours following the second exposure to enflurane anesthesia with subsequent elevation of liver enzymes, and the associated patchy hepatocellular necrosis with increased number of eosinophils in the portal tracts suggest this relationship. Furthermore, the heightened sensitization to enflurane may have been influenced by the prolonged use of chlorpheniramine maleate for control of the patient's asthma. This drug has been reported to cause induction of hepatic microsomal enzyme systems which has been suggested as being associated with increased hepatotoxicity of halogenated hydrocarbons[8]. Indeed, this

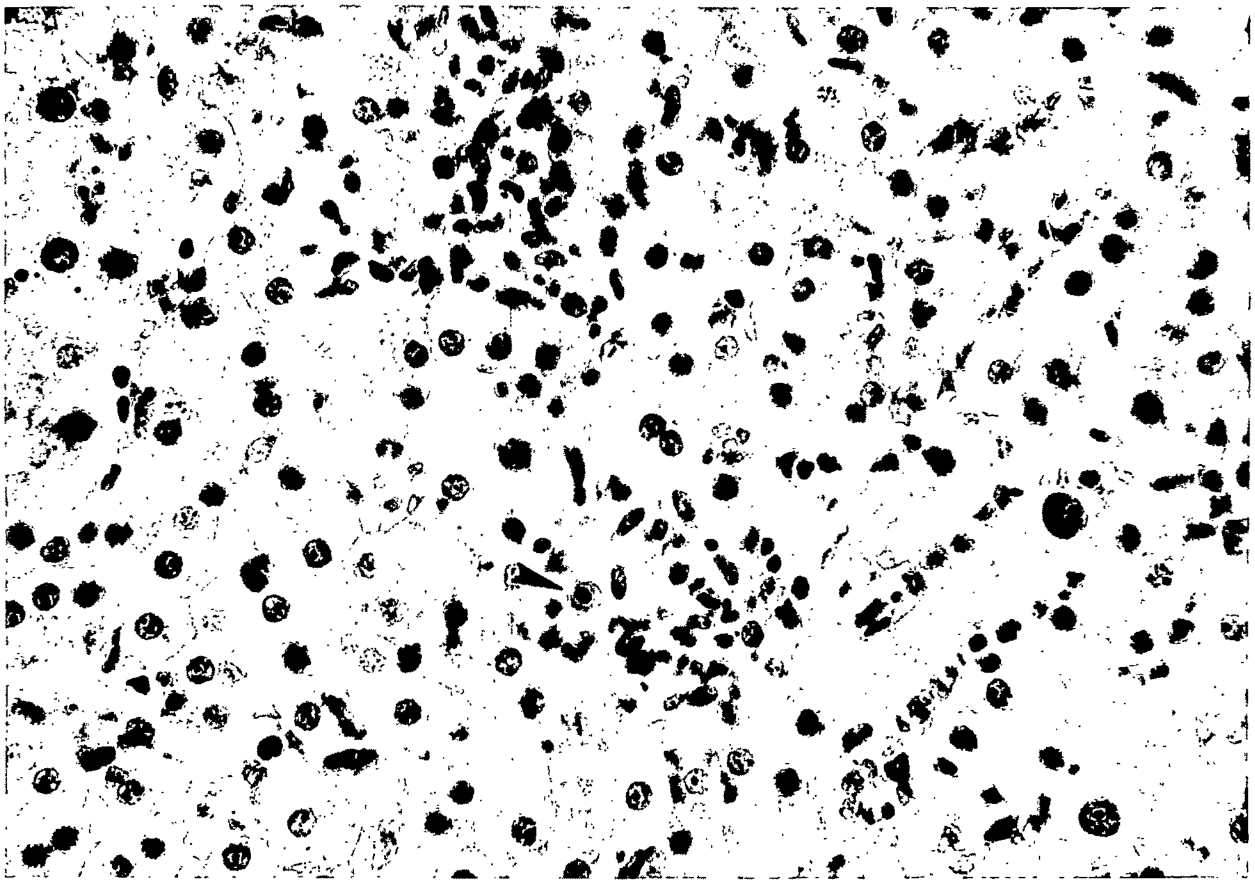


FIG 2. Higher magnification of an area of necrosis with acidophilic body showing pyknotic nucleus (arrow) Hematoxylin and eosin; ×100.

relationship was suggested by Reynolds et al,[9] in their report of one patient who had been receiving phenobarbital and diphenylhydantoin and who developed fulminant massive hepatic necrosis following fluroxene anesthesia. However, Greene[10] failed to demonstrate an increase in halothane-induced hepatitis in 117 patients who were receiving phenobarbital at the time of repeated exposure to halothane. Thus, his study suggested that under clinical conditions hepatic microsomal enzyme induction in man may bear no relation to hepatotoxicity of halogenated anesthetics.

The absence of either hypotension during surgery, or hypoxia or hepatitis B antigen in serum, and the fact that no blood products were administered excluded these factors as possible causes of hepatic injury. There was no evidence of sepsis as the scalp wound was not infected; multiple blood and urine cultures were negative and the patient's febrile course spontaneously resolved in the absence of significant antibiotic coverage.

It is unlikely that the hypersensitivity reactions manifested in this patient were due to cephalothin. The patient did not have an adverse reaction to either the cephalothin administered 7 years ago following her appendectomy or the cephalothin administered after the first operation during the present admission. In addition, no adverse effects were noted when cefamandole was given after she became febrile following the second operation. Sanders et al[11] reported that the serum sickness-like reactions to cephalothin are related to the administration of large doses of the drug by rapid intravenous infusion for a prolonged period. This was not the case in our patient. Although rare instances of transitory elevation of serum levels of transaminases have been reported after cephalosporins, hepatic injury is not a significant complication of this group of antibiotics.[12]

We did not rechallenge the patient with enflurane postoperatively to prove whether her hepatitis was in fact related to the enflurane. The severity of her symptoms, the prolonged recovery from hepatitis, and the possibility of precipitating severe hepatic damage led us to believe such a diagnostic test was not in order.

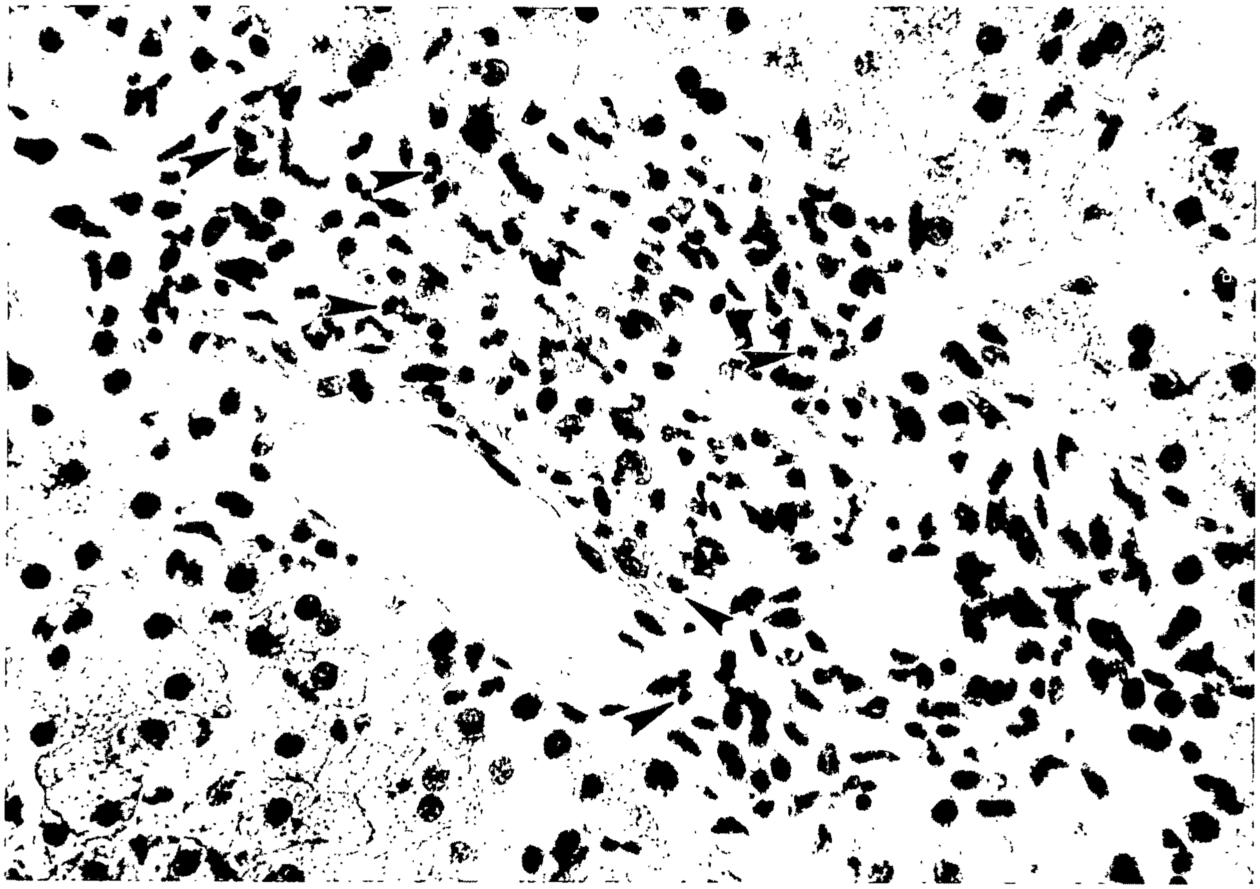


FIG 3. Portal tract showing edema and increased number of eosinophils (arrows) and increased mononuclear cell infiltration. Hematoxylin and eosin; ×100.

It is our conclusion that based on the clinical manifestations, biochemical changes, and typical histopathologic abnormalities, our patient developed enflurane hepatitis. Unlike previously reported cases, the characteristic histologic changes are demonstrated.

## REFERENCES

1. Lindenbaum J, Leifer E: Hepatic necrosis associated with halothane anesthesia. N Engl J Med 268:525–530, 1963
2. Joshi PH, Conn HO: The syndrome of methoxyflurane-associated hepatitis. Ann Intern Med 80:395–401, 1974
3. Harris JA, Cromwell TH: Jaundice following fluroxene anesthesia. Anesthesiology 37:462–463, 1972
4. Van der Reis L, Askin SJ, Frecker GN, et al: Hepatic necrosis after enflurane anesthesia. JAMA 227:76, 1974
5. Denlinger JK, Lecky JH, Nahrwold ML: Hepatocellular dysfunction without jaundice after enflurane anesthesia. Anesthesiology 41:86–87, 1974
6. Sadove MS, Kim SI: Hepatitis after use of two different fluorinated anesthetic agents. Anesth Analg 53:336–340, 1974
7. Tsang HS: Jaundice after enflurane anesthesia. IMJ 148:593–594, 1975
8. Zimmerman HJ: Hepatotoxicity. New York, Appeleton-Century-Crofts, 1978, pp 11–27
9. Reynolds ES, Brown BR, Vandam LD: Massive hepatic necrosis after fluroxene anesthesia—a case of drug interaction? N Engl J Med 286:530–531, 1972
10. Greene NM: Halothane anesthesia and hepatitis in a high-risk population. N Engl J Med 289:304–307, 1973
11. Sanders WE, Johnson JE, Taggart JG: Adverse reactions to cephalothin and cephapirin. N Engl J Med 290:424–429, 1974
12. Owens DR, Luscombe DK, Russell AD, et al: The cephalosporin group of antibiotics. Adv Pharmacol Chemother 13:83–172, 1975

ANESTH ANALG
59:150-153, 1980

# A Serious Anesthetic Hazard during Orthognathic Surgery

**Lennart Fagraeus, MD, PhD,***
**John C. Angelillo, DDS, MD,† and**
**Edward A. Dolan, DDS‡**

Oral surgical procedures for the correction of maxillomandibular deformities present unique anesthetic problems, which, though reported in oral surgical journals,[1-4] have not received sufficient attention in the anesthesiology literature. One of these unique problems relates to the fact that this type of surgery requires the extensive use of pneumatic saws and drills. The close proximity of the osteotomy sites to the airway, especially in maxillary surgery, presents the possibility that an endotracheal tube may be inadvertently damaged by the cutting instruments.

The purpose of this paper is to apprise anesthesiologists of this potential hazard by presenting an unusual case in which both nasotracheal and pilot tubes were cut in the nasopharynx during maxillary segmental osteotomy.

## Case Report

A healthy 35-year-old woman was admitted to the oral surgery service for correction of bimaxillary protrusion by maxillary and mandibular anterior segmental osteotomies.

General anesthesia was induced with sodium thiopental followed by topical tracheal instillation of lidocaine and succinylcholine chloride intravenously. Nasal intubation with a 7-mm endotracheal tube was performed without difficulty under direct vision. Anesthesia was maintained with nitrous oxide, oxygen, and incremental doses of fentanyl and pancuronium bromide.

One hour and 15 minutes after the start of surgery, it was noticed that the ventilator bellows suddenly collapsed as if the breathing circuit had suddenly become disconnected. Examination of the system did not reveal any mechanical malfunction. Manual ventilation was unsuccessful, and only after gas flows had been significantly increased could an effective tidal volume be obtained. Simultaneously the surgeons noted gas bubbling through the blood in the operating field apparently coming from the nasopharynx. The leak was sealed with throat packs and this maneuver provided a sufficiently tight airway, but when the nasotracheal tube was subsequently suctioned, a small amount of bright red blood was obtained. At this point, the maxilla was down-fractured and the portion of the endotracheal tube in the nasal cavity could be seen. It was obvious that the tube had been severely damaged. Because of the risk of aspiration of blood and also because it was anticipated that the procedure would require several more hours of anesthesia, it was decided to remove the damaged tube and reintubate the patient. The patient was ventilated with 100% $O_2$, the mouth and pharynx were suctioned, and the cuff deflated. Extubation proved, however, somewhat difficult. Closer examination of the nasotracheal tube revealed that it had been almost completely severed and that the pilot tube had melted and its lumen had become occluded so that the cuff remained inflated (Figs 1 and 2). Subsequent nasal reintubation was performed without difficulty.

The surgical drapes, which had been previously removed during the reintubation, were replaced and the procedure was completed uneventfully. At the end of the operation the patient was taken to the recovery room awake with the endotracheal tube in place since suctioning of the nasotracheal tube yielded a moderate amount of clotted blood. Vital signs remained stable but auscultation of the chest revealed scattered coarse rales throughout both lung fields which disappeared over the next few hours. An x-ray of the chest showed no infiltrate or atelectasis. The patient was extubated without difficulty the same evening.

## Discussion

Maxillofacial surgical procedures for correction of deformities are almost exclusively performed under general anesthesia, usually with nasotracheal instead of orotracheal intubation.[5-7] Despite the anesthetic problems associated with this type of surgery there is remarkably little on the subject in the anesthetic literature. Indeed, only one case report dealing with anesthetic complications has been published in an anesthesia journal[8]; in this case a nasotracheal tube was transfixed by a Kirschner wire.

While it is imperative that the anesthesiologist provide a secure and uninterrupted airway both during surgery and during recovery from anesthesia, minimal infringement of the surgical field is also essential. In addition to this competition for the airway, the nature of the surgical procedures requires that bone cuts be made adjacent to the endotracheal tube on both its medial and lateral sides (Figs 3 and 4). The proximity

---

* Associate Professor, Department of Anesthesiology.

† Assistant Professor, Chief, Division of Oral Surgery.

‡ Assistant Professor, Division of Oral Surgery.

Received from the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina 27710. Accepted for publication September 24, 1979.

Reprint requests to Dr. Fagraeus.

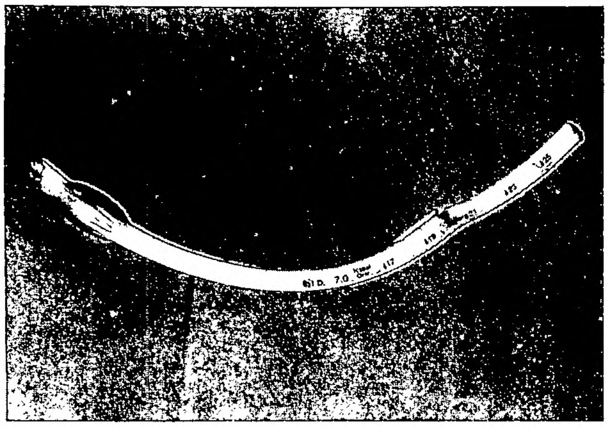


FIG 1. Endotracheal tube with incision made by the cutting instrument. Note the severed pilot tube and the still inflated cuff.

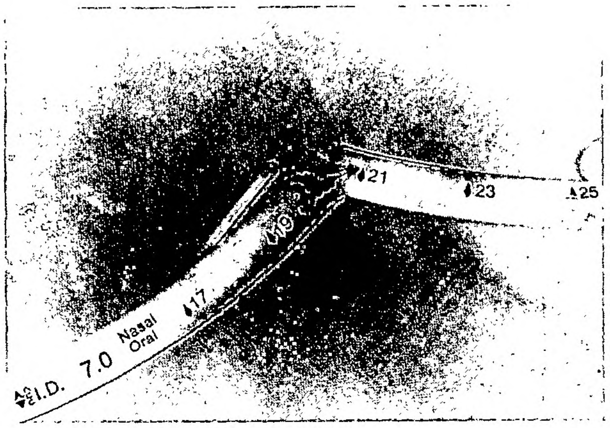


FIG 2. Close view of the almost completely transected endotracheal tube and the occluded pilot tube.

of the endotracheal tube to the osteotomy sites in a restricted area creates a situation in which accidental damage to the endotracheal tube can easily occur. Seven cases with complications similar to ours have been reported in the oral surgery literature.[1-3] In three of these cases, both nasotracheal and pilot tubes were severed; in three, only the pilot tube was cut; in one, the esophageal stethoscope was cut. In all cases the anesthetic equipment was damaged adjacent to an osteotomy site and the cutting instrument was directed posteriorly either on the lateral wall or in the floor of the nasal cavity (Figs 3 and 4).

Once the endotracheal tube or the pilot tube has been damaged either the patient must promptly be reintubated or an acceptable airway must be established by sealing around the nasotracheal tube with throat packs. While the decision may be one of personal judgment and related to experience, several factors need to be considered.

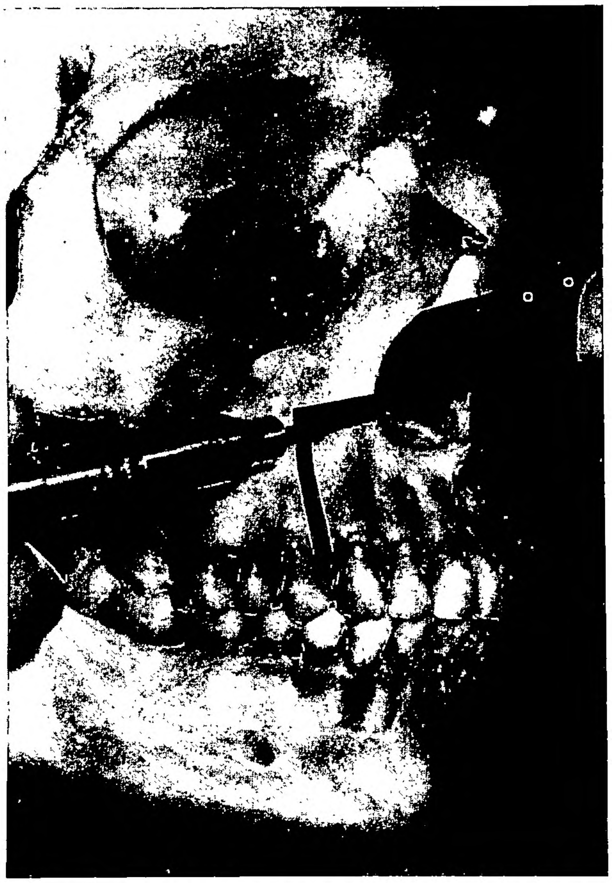


FIG 3. View of lateral maxillary osteotomy (black line) demonstrating the close proximity between cutting instrument and nasotracheal tube.

The extent of damage to the tube, the amount of surgery yet to be completed, and the circumstances of the surgical field need to be evaluated. Sealing the tube with throat packs may be appropriate if the leak is small and easy to localize, or if the procedure is near its end. However, inspection of the damage may be impossible since the tube may have been cut deep in the nasopharynx and the site of the leak may not be readily apparent. In such a situation sealing around the tube with throat packs may be difficult if not impossible. On the other hand, the surgical procedure cannot be terminated since the maxilla may already be divided and "floating," a situation which might make reintubation extremely difficult. If nasal reintubation is difficult or not possible, an orotracheal tube can be inserted and either left in place for the remainder of the surgical procedure and recovery period or later removed when nasal intubation is possible. If orotracheal intubation cannot be performed, emergency measures must be considered, e.g., insufflating 100% $O_2$ through a large bore cannula

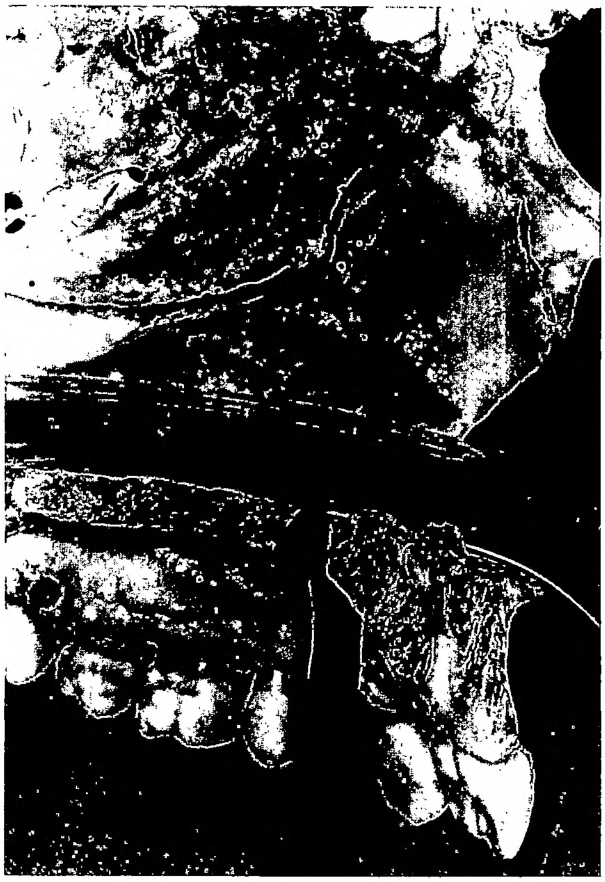


FIG 4. Medial aspect of same osteotomy (black line) as in Fig 3. Note proximity of the osteotomy both below and behind the translucent nasotracheal tube.

inserted through the cricothyroid membrane and/or tracheostomy.

In our case reintubation was necessary because the incident took place in the early stages of the procedure and because blood was seeping into the severed nasotracheal tube. Extubation was difficult partly because the cutting had severed all but a tenuous bridge of the tube wall (Fig 1). In addition, when the pilot tube was closely examined, it was obvious that the heat from the drill had melted and divided it (Fig 2), thereby occluding both distal and proximal parts leading to the surprise finding of an undeflated cuff upon extubation. Several reports have been presented regarding the inability to deflate cuffed endotracheal tubes, a complication that is apparent and easily recognized in all cases of orotracheal intubation.[9-13] With an orotracheal tube resistance to withdrawal is more unusual and hence more obvious than with a nasotracheal tube with which resistance is often significant because of the narrow passages in the nasal cavity. Fortunately our patient did not have hoarseness, sore throat, or nasal complications after the incident; her convalescence was uneventful.

Following damage to the nasotracheal or pilot tube, aspiration of blood, secretions, foreign particles, or bone spicules greatly increase the possibility of atelectasis and pneumonitis. To decrease the risk of aspiration following a leak in the sealed airway the patient should immediately be placed in a moderate Trendelenburg position (30°), thus reversing gravitational influence and invasion of the trachea by blood and secretions. To reduce the risk of aspiration it would seem prudent to perform these oral surgery procedures in a slight head-down tilt position (5 to 15°) and to utilize pharyngeal packs as suggested by Love.[14] Further support for use of the slight head-down position and packs during this type of surgery can be found in studies showing that even properly inflated endotracheal cuffs do not protect against aspiration.[15-18] Finally, if aspiration is suspected or cannot be ruled out, repeated auscultation and chest x-rays are mandatory in the immediate postoperative period.

Several instruments have been designed to protect endotracheal tubes from being damaged during orthognathic surgical procedures.[2,4] Stainless steel guards fashioned from spatulas, malleable retractors, or metallic tube protectors have been found to work very well.

During orthognathic surgical procedures protection and maintenance of the airway is the responsibility of both the surgeon and the anesthesiologist. The oral surgeon must be constantly aware of the spatial relationships of his instruments so as to avoid interruption of the airway. The anesthesiologist must be prepared to act with speed and determination to reestablish a satisfactory airway should it become impaired.

## REFERENCES

1. Tsueda K, Carey WJ, Gonty AA, et al: Hazards to anesthetic equipment during maxillary osteotomy: report of cases. J Oral Surg 35:47, 1977
2. Pagar DM, Kupperman AW, Stern M: Cutting of nasoendotracheal tube: an unusual complication of maxillary osteotomies. J Oral Surg 36:314–315, 1978
3. Mosby EL, Messer EJ, Nealis MF, et al: Intraoperative damage to nasotracheal tubes during maxillary surgery. J Oral Surg, 36: 963–964, 1978
4. Hought R, Zallen RD, Nathan R: Use of a metallic nasal tube protector during maxillary osteotomy. J Oral Surg 36:977, 1978
5. Collins VJ: Endotracheal anesthesia with sodium Pentothal for maxillofacial surgery: report of 48 cases. Anesthesiology 9:62–72, 1948
6. Makel HP, Major MC, Pou LH Jr, et al: Anesthesia in maxillofacial surgery. Anesthesiology 14:498–504, 1953
7. Davies RM, Scott JG: Anaesthesia for major oral and maxillofacial surgery. Br J Anaesth 40:202–208, 1968

8. Lee, C, Schwartz S, Mok MS: Difficult extubation due to transfixation of a nasotracheal tube by a Kirschner wire. Anesthesiology 46:427, 1977
9. Davies RM: Faulty construction of a reinforced latex endotracheal tube. Br J Anaesth 35:128–130, 1963
10. Gould AB Jr, Seldon TH: An unusual complication with a cuffed endotracheal tube. Anesth Analg 47:239–240, 1968
11. Hedden M, Smith RBF, Torpey DJ: A complication of metal spiral-imbedded latex endotracheal tubes. Anesth Analg 51: 859–862, 1972
12. Tavakoli M, Corssen G: An unusual case of difficult extubation. Anesthesiology 45:552–553, 1976
13. Stirt JA, Kaufman RD: Hazard associated with armored endotracheal tube. Anesth Analg 57:381, 1978
14. Love SHS: The danger of inhalation of debris during anesthesia. Br Dent J 118:503–508, 1963
15. Mehta S: The risk of aspiration in presence of cuffed endotracheal tubes. Br J Anaesth 44:601–605, 1972
16. Egnatinsky J: Overinflating low-pressure cuffs to prevent aspiration. Anesthesiology 42:114, 1975
17. Pavlin EG, Van Nimwegan D, Hornbein TF: Failure of a high-compliance low-pressure cuff to prevent aspiration. Anesthesiology 42:216–219, 1975
18. Mostert JW: Cuffs do not seal the trachea airtight. Anesthesiology 46:309–310, 1977

---

## Streptokinase in Acute Myocardial Infarction

In a controlled trial of streptokinase in acute myocardial infarction, 512 of 2338 patients at 11 European centers were stratified according to clinical severity. Three hundred fifteen patients allocated to medium-risk and high-risk groups were randomized to a 24-hour infusion of streptokinase or glucose. There were no essential differences in the severity of illness in the two groups before infusion. The overall mortality rates within 6 months were significantly lower ($p < 0.01$) in the streptokinase group (15.6%) than in the control group (30.6%). Bleeding complications were more frequent in the streptokinase group, but except for two nonfatal cerebral hemorrhages these complications were clinically unimportant. The treatment was generally well tolerated. It is concluded that streptokinase given under the conditions of this trial, to medium-risk patients admitted to a coronary-care unit within 12 hours of onset of symptoms, reduced mortality at 6 months. (*European Cooperative Study Group for Streptokinase Treatment in Acute Myocardial Infarction: Streptokinase in acute myocardial infarction. N Engl J Med 301:797–802, 1979*)

*See Also—Sullivan JM: Editorial. Streptokinase and myocardial infarction. N Engl J Med 301:836–837, 1979.*

ANESTH ANALG
59:154-156, 1980

# Dangerous Rise in Pulmonary Wedge Pressure following Aortography in a Patient with a Pheochromocytoma

**J. J. Rouby, MD, G. Gory, MD, T. Gaveau, MD, P. Glaser, MD, and P. Viars, MD**

Many authors have reported the high incidence of hyertensive crises following translumbar aortography for localization of pheochromocytomas.[1-3] In 1968, Rossi et al,[4] after a survey of 99 cases, suggested that the preoperative control of blood pressure with phenoxybenzamine and the use of a femoral catheterization technique could minimize the hazards of the procedure. We report a patient with a pheochromocytoma in whom a dramatic increase in the pulmonary wedge pressure occurred immediately following femoral aortography in spite of pharmacologic preparation with phenoxybenzamine.

## Case Report

A 32-year-old housewife suffered from occasional palpitations, throbbing headaches, and anxiety during her second pregnancy. At the 22nd week, her blood pressure varied from 150/100 to 250/130 mm Hg. There was no albumin in her urine; an electrocardiogram showed left ventricular strain and funduscopic examination revealed papilledema and a marked bilateral arteriolar narrowing. As the patient failed to respond to antihypertensive therapy, a pheochromocytoma was suspected and later confirmed by elevated urinary levels of normetanephrine, 13 mg/24 hours (normal, <4 mg/24 hours). At 33 weeks a live baby was vaginally delivered after an induced labor. On this occasion, her blood pressure rose to 250/150 mm Hg and the patient was successfully treated with sodium nitroprusside.

She was admitted to the hospital several weeks later for surgical excision of the pheochromocytoma. Her general condition was unchanged and the paroxysmal symptoms had remained the same. The red blood cell volume, measured by the standard dilution technique using $^{51}$Cr-labeled autologous red cells, was in the normal range (24 ml/kg). So, too, was the plasma volume (43 ml/kg) calculated from the red blood cell volume and the arterial hematocrit. During the 10 days preceding the operation, blood pressure was controlled with oral phenoxybenzamine (1 mg/kg). In the immediate preoperative period femoral angiography was undertaken to localize the tumor. This was performed under deep neuroleptanalgesia (Table) and included aortography (55 ml of 65% angiografine injected with a power syringe at a pressure of 6 kg/cm$^2$ and a speed of 1.5 seconds), followed 25 minutes later by selective arteriography (5 ml of 65% angiografine manually injected). An arterial cannula and a Swan-Ganz thermistor catheter had been inserted after induction of anesthesia. Heart rate, systolic, diastolic, and mean arterial and pulmonary wedge pressures were recorded on a Thompson multi-channeled monitor with a Statham P23 transducer. Cardiac output was measured in triplicate by the thermodilution technique using an Edwards apparatus (no. 9500) after injections into the right atrium of 10 ml of a 2.5% glucose solution at 0 C. The following were calculated:

$$(\text{CI L/min} \times \text{m}^2) = \text{CO/body area}$$

$$(\text{TVR units/m}^2) = (\text{MAP} - \text{CVP})/\text{CI}$$

$$(\text{LSWI g/m}^2) = \frac{13.6 \times (\text{MAP} - \text{PWP}) \times \text{CI}}{\text{HR}}$$

where CI = cardiac index; CO = cardiac output; TVR = total vascular resistance; MAP = mean arterial pressure; CVP = central venous pressure; LSWI = left stroke work index; PWP: pulmonary wedge pressure; and HR = heart rate. These data were recorded before the procedure (control, C) 2 and 15 minutes after aortography (A), and 2 and 15 minutes after selective arteriography (SA).

As shown in Fig 1, arterial hypertension and slowing of the heart rate occurred after both the aortography and the selective arteriography. Arterial pressure remained elevated after the arteriography (205/100 mm Hg) and was lowered with a 1 μg/kg/min infusion of sodium nitroprusside. While the pressor response related to the aortography was due to a moderate increase in TVR (from 27 to 31 units/m$^2$) associated with an increase in CI (from 3.8 to 4.91/min × m$^2$), marked elevation of TVR (from 33 to 43 units/m$^2$) was largely responsible for the arterial hypertension following the selective arteriography (Fig. 2).

As shown in Fig 3, LSWI increased after both aortography and arteriography (95 g/m$^2$). A dramatic

---

Received from the Department of Anaesthesia, Pitie-Salpetriere Hospital, 83, boulevard de l'hôpital, 75634-Paris Cedex 13, France. Accepted for publication October 1, 1979.

Reprint requests to Dr. Rouby.

**TABLE**

**Anesthetic Technique Used for Angiography***

| | |
|---|---|
| Premedication | |
| Droperidol | 20 mg IM |
| Phenoperidine | 1 mg IV |
| Induction (duration, 30 minutes) | |
| Droperidol | 20 mg IV |
| Phenoperidine | 5 mg IV |
| Diazepam | 10 mg IV |
| Nasotracheal intubation | |
| Topical anesthetization of the pharynx and the larynx with 5% lidocaine (duration 10 minutes) preceding nasotracheal intubation. | |
| Maintenance of anesthesia | |
| Droperidol | 15 mg IV |
| Phenoperidine | 3 mg IV |
| Diazepam | 10 mg IV |
| Pancuronium | 6 mg IV |
| 60% $N_2O$/40% $O_2$ | |
| Mechanical ventilation | |

* Patient's weight = 55 kg; duration of anesthesia = 120 minutes.

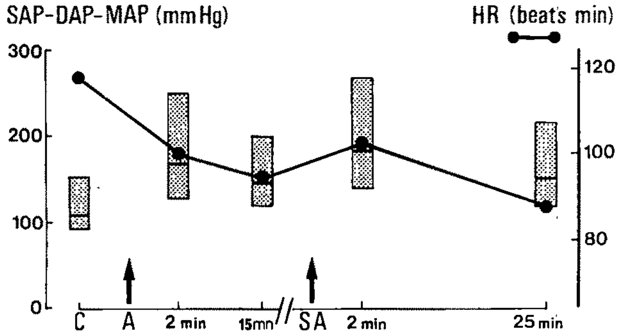


FIG 1. Systolic, diastolic, and mean arterial pressures (SAP, DAP, MAP, respectively) and heart rate (HR) before injection of contrast material (C), 2 and 15 minutes after aortography (A), and 2 and 25 minutes after selective arteriography (SA) (top of stippled rectangle, SAP; bottom, DAP; horizontal line in rectangle, MAP).

increase in PWP from 7 to 25 mm Hg occurred during the 2 minutes following the aortic injection. The PWP spontaneously returned to 13 mm Hg in the next 15 minutes, remained stable immediately after the selective arteriography, and then decreased to 8 mm Hg 25 minutes later. Selective arteriography showed the tumor to be in the lower pole of the left kidney. The tumor (140 g) was removed through a left flank incision 1 hour after the x-ray procedures. During surgical manipulations, the blood pressure was controlled with sodium nitroprusside with monitoring of pulmonary wedge pressure and cardiac output to assure optimal volume loading. The patient had an uncomplicated recovery and has remained well with blood pressure in the normal range.

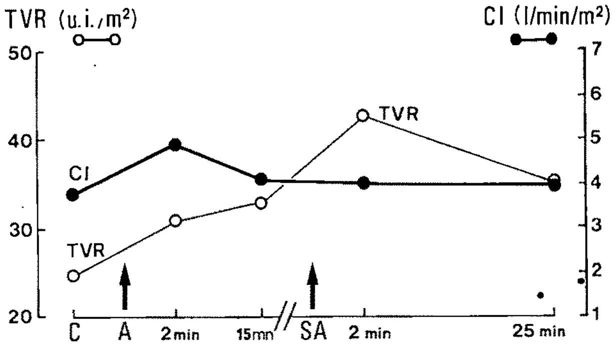


FIG 2. Total vascular resistance (TVR) and cardiac index (CI) before injection of contrast material (C), 2 and 15 minutes after aortography (A), and 2 and 25 minutes after selective arteriography (SA).

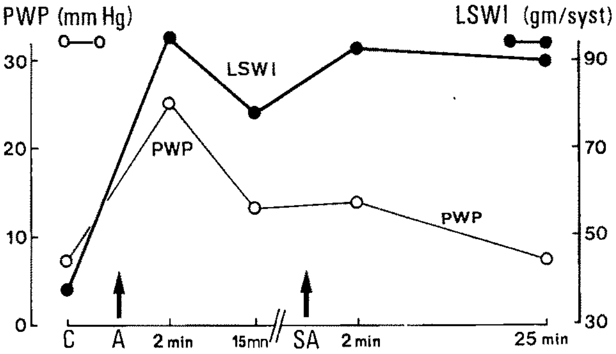


FIG 3. Pulmonary wedge pressure (PWP) and left stroke work index (LSWI) before injection of contrast material (C), 2 and 15 minutes after aortography (A), and 2 and 25 minutes after selective arteriography (SA).

## Discussion

Arterial hypotension and peripheral vascular dilation are usually observed after high-pressure injection of contrast media in the aortic root.[5] In this patient arterial hypertension with elevation of the cardiac index and total vascular resistance followed the two angiographic injections. This suggests that the radiopaque material may have stimulated an outpouring of large amounts of pressor substances into the general circulation.

The cardiac effects of this pressor response were different after the injections of contrast material into the aorta and into the arteries. Pulmonary wedge pressure increased to a level known to be associated with onset of pulmonary edema when the contrast material was injected into the aorta but not when a smaller dose was used for the selective arteriography. The dangerous rise in pulmonary wedge pressure after the aortography may be related to a transient alteration in cardiac performance, possibly resulting from a direct myocardial toxic effect due to the presence of large amounts of contrast material.[6]

In conclusion, preoperative arteriographic localization of a pheochromocytoma can be hazardous despite use of a femoral approach, adequate preparation with phenoxybenzamine, and a sufficient depth of anesthesia. Pulmonary edema can occur during the aortic root injection if a transient myocardial depression is associated with hypertensive crisis. When such a procedure must be undertaken to localize a pheochromocytoma use of vasodilating drugs may be indicated during the 15 minutes following the injection of contrast material, especially when large amounts are used. Brief infusion of sodium nitroprusside is probably the method of choice for producing vasodilation because it is effective, rapid in onset, and short in duration.[7]

## REFERENCES

1. Sjoerdsma A., Engelman K, Waldmann TA, et al: Pheochromocytoma: current concepts of diagnosis and treatment. Ann Intern Med 65:1302–1326, 1966
2. Koonce DH, Pollock BE, Glassy FJ: Bilateral pheochromocytoma associated with neurofibromatosis: death following aortography. Am Heart J 44:901–909, 1952
3. Lopez JF: Pheochromocytoma of the adrenal gland with granulosa cell tumor and neurofibromatosis: report of a case with fatal outcome following abdominal aortography. Ann Intern Med 48:187–199, 1958
4. Rossi P., Young IS, Panke WF: Techniques, usefulness and hazards of arteriography of pheochromocytoma: review of 99 cases. JAMA 205:547–553, 1968
5. Karliner JS, Bouchard RJ, Gault JH: Haemodynamic effects of angiographic contrast material in man: a beat by beat analysis. Br Heart J 34:347–355, 1972
6. Gootman N, Rudolph A, Buckley NM: Effects of angiographic contrast media on cardiac function. Am J Cardiol 25:59–65, 1970
7. El-Naggar M, Suerte E, Rosenthal E: Sodium nitroprusside and lidocaine in the anesthetic management of pheochromocytoma. Can Anaesth Soc J 24:353–360, 1977

---

## Postoperative Ulnar Neuropathy

Although compressive ulnar neuropathy developing during surgical procedures under general anesthesia has been recognized, clinical and electrophysiologic features of this neuropathy have been incompletely described. This report describes the course of eight patients with this complication, mainly following intra-abdominal or intrathoracic operations. Neuropathy was associated with a persistent severe deficit during a mean follow-up of 23.5 months (range, 6 to 96 months) after operation. Electrophysiologic studies verified substantial Wallerian degeneration in the majority of patients. Clinical and electrophysiological data, as well as intraoperative findings in some patients, suggest that compression occurred at the cubital tunnel. These patients with ulnar neuropathy had a particularly poor prognosis, whether treated surgically (decompression or transposition) or medically. Prevention of ulnar nerve compression during surgery therefore assumes paramount importance. (*Miller RG, Camp PE: Postoperative ulnar neuropathy. JAMA 242:1636–1639, 1979*)

ANESTH ANALG
59:157-158, 1980

# Pruritis following Spinal Anesthesia

**David W. Koski, MD,* and**
**John G. Fraser, MD†**

Diabetic peripheral neuropathy is a frequent complication of diabetes mellitus. The neuropathy is not necessarily proportional to the duration or severity of the disease.[1] The following case report deals with the temporary exacerbation of neuropathic symptoms after spinal anesthesia.

## Case Report

A 37-year-old man was admitted for treatment of a diabetic ulcer over the third and fourth metatarsal-phalangeal joints of his right foot. He gave an 11-year history of diabetes mellitus and was well controlled on 20 units of NPH insulin daily and a 2200-calorie (A.D.A.) diet. Because of his poor response to local treatment and antibiotics, the patient was scheduled for a ray amputation of the third toe. During the preanesthetic evaluation, the patient stated that he had had an "allergic reaction to Xylocaine" 2 months previously. The record of the patient's previous hospitalization showed that he had received a field block with lidocaine for debridement of the same foot ulcer and this had been followed by intense itching at the operative site. Skin changes were not noted, the reaction was not treated, and the itching subsided spontaneously after 3 hours. In the past, the patient had local anesthetics for dental restoration without incident.

On the day of operation, the patient received preoperative sedation consisting of secobarbital (150 mg) and morphine sulfate (10 mg) intramuscularly. In the operating room, the patient was placed in the left lateral decubitus position and the skin was prepared for spinal anesthesia with Betadine solution. Skin anesthesia over the L3-L4 interspace was produced with 0.5 ml of 1% procaine. A satisfactory dural tap was performed with a 22-gauge diamond point spinal needle. Eleven milligrams of tetracaine with 1.1 ml of 10% dextrose was then injected, with a prompt onset of anesthesia and a sensory blockade to the level of the tenth thoracic dermatone. The limited foot amputation proceeded without incident, and the patient was transferred to the recovery room. His vital signs were stable. Approximately 60 minutes after admission to the recovery room, he began to complain of intense itching in a stocking distribution of both feet with some patchy extensions toward his knees. No skin changes were visible. When the patient's discomfort became so great that he required physical restraint to keep him from excoriating his feet, he was given diphenhydramine, 50 mg IM, which was without effect. Diazepam, 7.5 mg IV, was necessary to sedate him and thereby control his agitation. The itching subsided gradually over the subsequent 6 hours.

On further questioning, the patient admitted to similar but mild episodes of itching and burning in the same distribution while at home. These had occurred several times in the previous 6 months and lasted approximately 30 minutes. The patient had not sought treatment for these sensations. Physical examination revealed all lower extremity pulses to be symmetrical and strong. Achilles tendon reflexes were symmetrically diminished but present. Temperature sensation was normal on the left but decreased on the right. Perception of pain was intact but proprioception and vibratory sensation were diminished bilaterally.

Electromyography and nerve conduction studies on the third postoperative day showed moderately severe to severe sensory motor polyneuropathy due to segmental demyelination. These changes were thought to be secondary to the patient's diabetes mellitus.

## Discussion

True allergic reactions to local anesthetics are rare,[2] yet the anesthesiologist is commonly presented with patients who claim to be allergic to these drugs. Hypersensitivity, overdose, and intravascular injection are responsible for many supposed allergic reactions.[2] We did not feel that this patient represented any of these categories and rejected the intradermal skin test to evaluate him further because of its reported lack of specific and clinically relevant information.[3]

Symmetric diabetic polyneuropathy is the most frequently seen diabetic neuropathy.[4] Common signs include loss of Achilles tendon reflexes and diminished or lost perception of pain, proprioception, vibration, and light touch. Symptoms can occur at any time during the progression of the disease and generally last 3 to 6 months. These can include pain, hypesthesia, and paresthesia. The neuropathy appears to result from metabolic damage to Schwann cells and the myelin sheath. The neuropathy is not related to the severity of carbohydrate intolerance and can oc-

---

* Senior Resident.

† Assistant Professor.

Received from the Department of Anesthesiology, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106. Accepted for publication October 1, 1979.

Reprint requests to Dr. Koski, Department of Anesthesiology, War Memorial Hospital, 500 Osborn Blvd., Sault Ste. Marie, MI 49783.

cur, even before carbohydrate intolerance is clinically apparent.[4]

This case demonstrates that severe and unusual symptoms may result during the return to full sensation following spinal anesthesia in a diabetic patient with peripheral neuropathy. Mild paresthesias are normally common during the return to full sensation. Because of his neuropathy, the patient may have perceived the paresthesias as extremely irritating itching. This premise is consistent with the concept that pruritus and formication result from minimal repetitive stimuli transmitted over pain pathways.[5] After spinal anesthesia in diabetic patients with neuropathy, these stimuli may cause pruritus which may be confused with an allergy. Nerve conduction studies may assist in identifying the pathogenesis.

### REFERENCES

1. Colby AO: Neurologic disorders of diabetes mellitus. Diabetes 14:424–429, 1965
2. Sadove M, Wyant G, Gittelson L, et al: Classification and management of reactions to local anesthetic agents. JAMA 148: 17–22, 1952
3. Incaudo G, Schatz M, Patterson R, et al: Administration of local anesthetics to patients with a history of prior adverse reaction. J Allergy Clin Immunol 61:339–445, 1978
4. Beisswenger PJ: Neuropathic and vascular complications occurring in diabetes mellitus. Postgrad Med 59:169–174, 1976
5. Sweet WH: Pain, in Handbook of Physiology, J Field (ed), Sect 1: Neurophysiology, vol 1, pp 498–499, Washington, DC, American Physiological Society, 1959

---

## Intra-aortic Balloon Pump

The treatment of 63 of 1,738 adult patients undergoing cardiac operations included insertion of an intra-aortic balloon pump (IABP). The clinical information available for the total group was analyzed retrospectively to reevaluate the indications for the IABP during cardiac surgery and to assess its hemodynamic effects. The incidence of use of the IABP decreased from 6.13% of cases at the first of the series (early 1976) to 1.73% of cases in late 1977. One third of the IABP insertions were before cardiopulmonary bypass, two thirds after bypass. Pre-bypass indications included complicated acute myocardial infarction, poor left ventricular function or shock, and combined coronary and valvular heart disease. Of 21 patients 17 (81%) survived. Post-bypass IABP insertion was indicated by a profound low cardiac output state, after maximum pharmacologic inotropic therapy. Of the 42 patients 26 (62%) survived. Detailed hemodynamic measurements were made in 11 patients. The IABP decreased systolic blood pressure, left and right ventricular filling pressures, and peripheral resistance, while it increased diastolic and mean arterial pressures, stroke work, cardiac output, and the endocardial viability ratio. The intra-aortic balloon was shown to be life-saving in certain patients. However it should only be used selectively for specific indications. Careful surgical and anesthetic management with good monitoring can be used in many patients instead of the balloon. (*Kaplan JA, Craver JM, Jones EL: The role of the intra-aortic balloon in cardiac anesthesia and surgery. Am Heart J 98:580–586, 1979*)

ANESTH ANALG
59:159-160, 1980

# Hydromediastinum after Placement of a Thermodilution Pulmonary Arterial Catheter

**Elaine P. Gordon, MD,***
**Stuart F. Quan, MD,† and**
**Richard M. Schlobohm, MD‡**

Flow-directed pulmonary artery catheters are used to monitor the hemodynamic status of critically ill patients.[1, 2] Although morbidity has been minimal,[3, 4] complications have included arrhythmias and conduction disturbances, knotting of the catheter, rupture of the pulmonary artery, pulmonary infarction, venous thrombosis, and infection.[3-5] This report describes an unusual complication of using such a catheter.

## Case Report

A 25-year-old Oriental woman was transferred to the intensive care unit of San Francisco General Hospital following labor and delivery complicated by premature rupture of the membranes, chorioamniotis, and postpartum hemorrhage. Physical examination in the intensive care unit revealed a pale woman with a small body habitus (height: 148 cm; pregravid weight: 40 kg). Respirations were 40/min, apical pulse was 150/min, and blood pressure was not obtainable by sphygmomanometry. Central pulses were barely palpable, and the extremities were poorly perfused.

The patient was felt to be in profound shock as a result of sepsis and postpartum hemorrhage. To optimize volume replacement, a #7F thermodilution flow-directed pulmonary arterial catheter (Swan-Ganz, Edwards Laboratories; Santa Ana, California) was inserted without difficulty using the central approach to the right internal jugular vein which results in the catheter traversing the skin just above the clavicle.[6] A pulmonary artery occlusion pressure (PAOP) was obtained on inflation of the balloon with 1.5 ml of air at a depth of 34 cm. A chest x-ray confirmed the catheter to be in a good central position. Initial PAOP was 1 to 2 torr. Central venous pressure (CVP) tracings measured via the proximal port of the catheter showed good respiratory fluctuations with an initial value of 0 to 1 torr. Normal saline (300 ml) was administered through the proximal port while adequate peripheral intravenous access was being established. Thermodilution cardiac output determinations using iced 5% dextrose infused through the proximal port yielded inconsistent and exaggerated valves. With each injection the patient experienced a cold sensation in the right supraclavicular area. Further determinations were halted when a slight swelling was noted in this region. A second chest x-ray revealed widening of the superior mediastinum (Figure, left) and attempts to aspirate blood through the proximal port were unsuccessful. A third chest x-ray taken simultaneously with the injection of 3 ml of radiopaque contrast medium (Hypaque) via the proximal port revealed extravasation of contrast material into the mediastinum (Figure, right). The catheter was left in place, using only the distal port for hemodynamic measurements, and was removed on the 3rd day. The patient subsequently made an uneventful recovery.

## Discussion

With a pulmonary artery catheter PAOP is measured via the distal catheter port. The thermodilution catheter also has a proximal port located 30 cm from the distal tip which is used for injection of a thermal indicator for cardiac output determinations and which can be used for CVP measurements as well as for infusion of intravenous fluids. In the ordinary adult patient, the proximal port of the catheter, when inserted via the internal jugular vein, will lie in the superior vena cava or right atrium. As a result of a small body habitus and a low approach to the internal jugular vein, in our patient the proximal port was located at least partly outside of the vein. Fluids infused through this port were extravasated into subcutaneous tissue and the mediastinum, which explains the exaggerated cardiac output results and the abnormal chest x-ray findings several hours later. This could be a serious complication if irritating or essential medications are being infused.

Appropriate pressure tracings from the proximal and distal ports and a chest x-ray which demonstrates that the catheter is in the pulmonary artery usually

---

* Resident, Department of Medicine, Mount Sinai Hospital, Toronto.

† Fellow in Emergency Medicine, University of California, San Francisco.

‡ Associate Clinical Professor of Anesthesia, University of California, San Francisco.

Supported in part by grant 1229 from the Robert Wood Johnson Foundation, Princeton, New Jersey.

Received from the Department of Medicine-Mt. Sinai Hospital, Toronto, Ontario, Canada; Departments of Anesthesia and Medicine-Division of Emergency Medicine, University of California, San Francisco. Accepted for publication October 16, 1979.

Reprint requests to Dr. Quan, Division of Respiratory Sciences, University of Arizona, Tucson, AZ 85724.

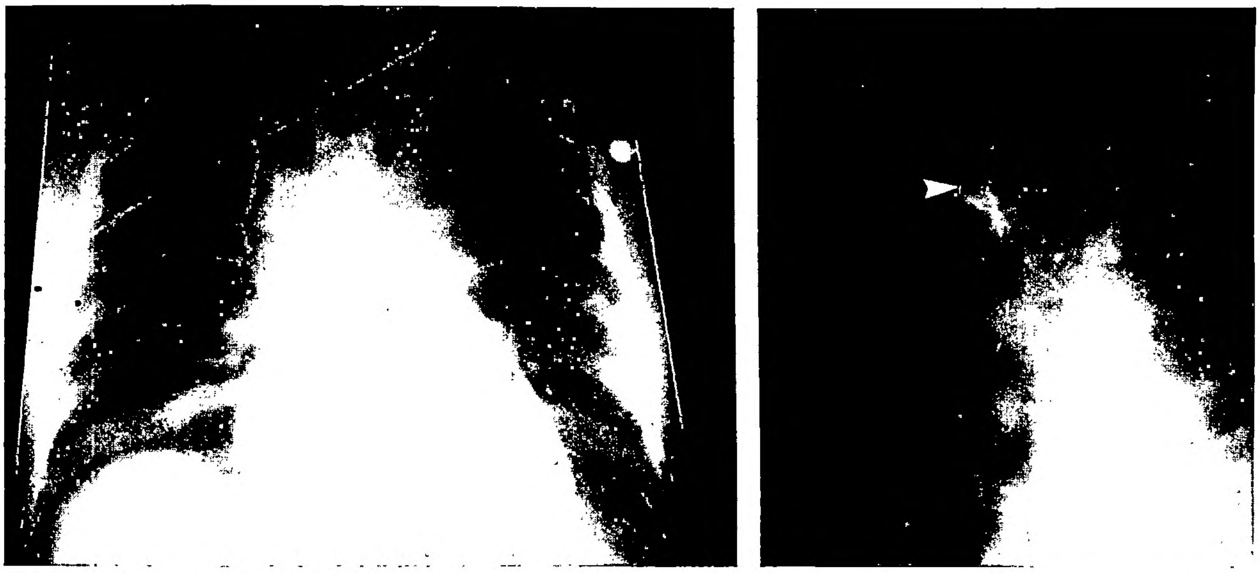


FIGURE. Radiographs demonstrating mediastinal widening and extravasation of contrast material. Left, widening of the superior mediastinum occurring after infusion of fluids via the proximal port of the catheter. Right, injection of contrast material via the proximal port results in extravasation into the mediastinum (arrow).

indicate that a pulmonary artery catheter is properly positioned. As illustrated in this case, however, when using the central approach to the internal jugular vein in a patient with a small body habitus, the proximal port of the catheter may be extravascular. Extravasation of fluid may be avoided if it is verified that blood can be aspirated from the proximal port prior to the infusion of intravenous fluids.

## ACKNOWLEDGMENT

The authors wish to express their appreciation to Ms. Susan Hay for her secretarial assistance.

## REFERENCES

1. Swan HJC, Ganz W, Forrester J, et al: Catheterization of the heart in man with the use of a flow directed balloon tipped catheter. N Engl J Med 283:447–451, 1970
2. Swan HJC, Ganz W: Use of balloon flotation catheters in critically ill patients. Surg Clin North Am 55:501–520, 1975
3. Pace NL: A critique of flow-directed pulmonary arterial catheterization. Anesthesiology 47:455–465, 1977
4. Katz JD, Cronau LH, Barash PG, et al: Pulmonary artery flow directed catheters in the perioperative period. JAMA 236:2832–2834, 1977
5. Dye LE, Segall PH, Russell RO, et al: Deep venous thrombosis of the upper extremity associated with the use of the Swan-Ganz catheter. Chest 73:673–675, 1978
6. Defalque RJ: Percutaneous catheterization of the internal jugular vein. Anesth Analg 53:116–121, 1974

# letters TO THE EDITOR

## Microwave Rewarming

To the Editor:

The application of microwave energy for rewarming after neonatal cardiac surgery with hypothermia and circulatory arrest, as proposed by Westenskow et al,[1] may eventually prove to be clinically useful. Before this can happen, however, there will have to be a greater understanding of both the thermal and nonthermal effects of high frequency electromagnetic radiation. The current assessment of the biologic effects of microwaves remains controversial.[2] In their article, Westenskow et al state "On the basis of extensive experience with the use of microwave heating for diathermy, it is unlikely that microwave rewarming as used in the present study is associated with tissue damage." This statement is supported by a reference published in 1965; this reference is nearly 15 years old in a field that is rapidly expanding. As early as 1967, Soviet scientists recognized direct and indirect central nervous system effects with low level microwave radiation[3] as well as nonthermal effects on the cardiovascular system. As a result of these discoveries, the Soviet Union set its level of safe exposure 1000 times lower than that of the United States.

While Westenskow et al state there was no evidence of myocardial injury on light microscopy, a more sophisticated and subtle method of detection might have employed creatine phosphokinase isoenzyme determinations. There is no assurance either that extended postoperative myocardial performance would not be affected. It would have been interesting to compare postoperative myocardial performance over several days in the microwave-treated group with a control population exposed only to conventional surface heating. The dielectric properties of tissues affect the absorbance of radiofrequency (RF) energy and consequently the heating patterns that develop. In tissues of high water content such as muscle or brain, absorption is high and the depth of RF penetration is relatively low. By comparison, in tissues of low water content, such as fat and bone, RF absorption is considerably less. In addition, interfaces separating tissues of different dielectric properties (high and low water content) can produce reflections, or severe standing waves of RF power, accompanied by "hot spots" that can be maximum in either tissue. In other words, resonance situations may occur as a result of special body and structural geometries and areas of thermal injury may occur in tissues other than those intended for rewarming. The confinement of microwave radiation can be difficult and reradiation may occur at unexpected anatomical sites.

The nonthermal effects of microwave radiation in biologic systems may include "pearl chaining," where blood elements in suspension in the presence of RF electromagnetic radiation may align themselves in chains parallel to the lines of force, much like iron filings about a magnet. In addition, dielectric saturation may occur resulting in the breakdown of hydrogen bonds in cellular proteins and enzymatic denaturation. Recent work has also demonstrated the injurious effects of microwaves on the ocular lens,[4] the human embryo,[5] and the electroencephalogram.[6]

We enjoyed reading this paper; however, in view of the immediate emphasis placed on the potential clinical application of the technique in neonates, more attention should be afforded to the possible deleterious effects of microwaves. A biologically immature organism, as the human neonate is, may be far more susceptible to the subtle effects of microwave radiation.

David Eric Lees, MD
*Anesthesiology Section*
William Schuette, EE
*Biomedical Engineering and Instrumentation Branch*
*National Institutes of Health*
*Bethesda, Maryland 20205*

REFERENCES

1. Westenskow DR, Wong KC, Johnson CC: Physiologic effects of deep hypothermia and microwave rewarming: possible application for neonatal cardiac surgery. Anesth Analg 58:297-301, 1979
2. Hazzard DG: Symposium on biological effects and measurement of radiofrequency/microwaves. Rockville, MD, Dept of Health, Education, and Welfare, 1977
3. Kholodov YA: The effect of electromagnetic and magnetic fields on the central nervous system. Washington, DC, NASA technical translation, TTF-465, 1967
4. Neelakantaswany PS, Ramakrishnan KP: Microwave-induced hazardous nonlinear thermoelastic vibrations of the ocular lens of the human eye. J Biomech 12:205-210, 1979
5. Neelakantaswamy PS: Microwave-induced injurious effects on the human embryo in utero. Biomed Tech 23:263-269, 1978
6. Bise W: Low power radio-frequency and microwave effects on human electroencephalogram and behavior. Physiol Chem Phys 10:387-398, 1978

To the Editor:

We appreciate the interest and comments of Dr. Lee and Mr. Schuette in regard to our publication on microwave rewarming following deep hypothermia to 20 C. There is no disagreement that this study represents an initial effort in data gathering for a possible clinical application of microwave energy. Since published reports have been primarily on the undesirable effects of whole body microwave irradiation, we hoped to find that localized irradiation to the myocardium for 1 to 2 hours might minimize possible side effects of chronic whole body microwave exposure, while the deep heat stimulates the hypothermic heart and warms the blood that circulates through the chambers.

In another phase of study we have not been able to demonstrate changes in blood chemistry and clotting times immediately following microwave rewarming. The creatine phosphokinase (CPK) isoenzymes could indeed provide a more subtle method of detecting myocardial damage. Preliminary studies in dogs show an increase in total CPK following hypothermia and rewarming, but insignificant change in the MB (heart muscle CPK) fractions between the hypothermic and normothermic (microwave rewarmed) animals. Long-term physiologic effects following localized microwave irradiation are another phase of study for the near future.

As in any institution where clinical research protocol in man must conform to the highest ethical and scientific standards, many biologic questions will need to be answered before this technique is attempted in man.

Dwayne R. Westenskow, PhD
*Assistant Professor*
K. C. Wong, MD, PhD
*Professor and Chairman*
*Department of Anesthesiology*
*University of Utah*
*College of Medicine*
*50 North Medical Drive*
*Salt Lake City, Utah 84132*

---

# Hazards of Scavenging Systems

To the Editor:

A series of clinical reports has recently appeared which highlights the importance of the negative pressure relief mechanism of waste anesthetic gas scavenging safety interfaces. A negative pressure relief mechanism is needed if the scavenging system is connected to a vacuum or active duct system. If the flow of vacuum exceeds the flow of waste gases leaving the anesthesia circuit, then the negative pressure relief mechanism should activate to entrain room air, thereby satisfying the vacuum flow and protecting the patient from withdrawal of anesthetic circuit gases. Some safety interfaces are "open" to the room and valveless so that air is easily entrained when vacuum flow exceeds waste gas flow. Unfortunately, if the waste gas flow exceeds the capacity of the suction to remove them, the waste gases spill out the opening, into the room, creating gas pollution. Because of the periodic nature (expiratory phase) of waste gas overflow, most "open" interfaces do not adequately protect personnel from pollution hazards.

The most common design emerging is the "closed" interface, which captures the waste gases, usually within a reservoir bag, until the vacuum flow can adequately remove them. Being a closed design unidirectional valves that allow the entrainment of room air must be provided so that the patient's lungs will not be subjected to negative pressure when the vacuum flow and the waste gas flow are not balanced. A common hazard reported with the North American Dräger and Foregger devices has been the malfunction of the negative pressure relief (pop-in) valve. In one instance the valve disc stuck in the closed position.[1] In the other report, the pop-in valve became covered and thus closed by a plastic bag so that gases could not be entrained.[2] In both instances, patients' lungs were subjected to negative pressure.

As a solution the authors of one article suggested the placement of additional air entry holes in the valve housing to protect against foreign matter closing the single intake hole. Instead, the manufacturer has provided a modification kit that will "stand-off" material that may occlude the single intake orifice.

The solution to all the problems reported thus far is a safety interface with two negative pressure relief valves, one to activate if the other fails. Since each valve can be of a different type, each can be designed to be free of any of the faults inherent in the design of the other, i.e., one can be a flutter valve, the other a spring-loaded disc.

By incorporating two negative pressure relief valves of different design features in a closed interface, safety and effectiveness can be obtained, provided the user is vigilant and services the equipment.

Ralph A. Milliken, MD
*Inter-Community Memorial Hospital*
*Newfane, New York 14108*

REFERENCES

1. Morr ZF, Stein ED, Orkin LR: A possible hazard in the use of a scavenging system. Anesthesiology 47:302-303, 1977
2. Patel KD, Dalal FY: A potential hazard of the Drager Scavenging Interface System for wall suction. Anesth Anal 58:327-328, 1979

---

# Bradycardia after Intravenous Fentanyl during Subarachnoid Anesthesia

To the Editor:

Although heart rate slowing is a well known side effect of narcotic administration, profound bradycardia is unusual. We recently observed heart rate slowing from 85 beats/min to 32 beats/min following administration of 50 μg of fentanyl intravenously to a 32-year-old 64 kg woman with a stable T5 sensory subarachnoid anesthetic for emergency appendectomy. This bradycardia was associated with a normal appearing P-R interval and a fall in blood pressure from 115/80 torr to 75/40 torr. Intravenous atropine, 0.8 mg, increased the heart rate to 95 beats/min and the blood pressure increased to 110/80 torr. The patient was awake and denied any dizziness or nausea.

Possible mechanisms for sinus bradycardia observed in this patient might include reflex heart rate slowing from peritoneal traction (celiac plexus reflex),[1] cardiac sympathetic nerve blockade,[2] and a parasympathetic effect produced by fentanyl.

A celiac plexus reflex seems unlikely since peritoneal manipulation was not occurring at the time of heart rate slowing.

The T5 sensory block was probably associated with only a partial block of the cardiac sympathetic nerves assuming an average sympathetic block about two dermatomes above the sensory level. Indeed the heart rate remained normal even after the T5 sensory level had been present for several minutes. Furthermore, the level of sensory anesthesia had not changed at the time of heart rate slowing. Therefore, it is unlikely that heart rate slowing was due to total cardiac sympathetic blockade.

The abrupt onset of bradycardia following injection of fentanyl suggested a drug-induced parasympathetic effect. Reitan et al,[3] noted a fairly abrupt decrease in heart rate following intravenous fentanyl in dogs and attributed this bradycardia to a drug-produced increase in vagal efferent impulses from the central nervous system. We speculate that the T5 sensory level resulted in only a partial cardiac sympathetic nerve blockade such that the heart rate remained normal. The subsequent injection of fentanyl abruptly increased the ratio of parasympathetic to sympathetic tone resulting in sinus bradycardia.

In conclusion, caution should be exercised when administering a vagomimetic drug like fentanyl during a high sympathetic block produced by subarachnoid anesthesia.

John C. Hilgenberg, MD
*Assistant Professor*

Walter C. Johantgen, MD
*Anesthesia Resident III*
*Department of Anesthesia*
*Indiana University School of Medicine*
*Indianapolis, Indiana 46223*

REFERENCES

1. Rocco AG, Vandam LD: Changes in circulation consequent to manipulation during abdominal surgery. JAMA 164:14-18, 1957
2. Greene NM: Physiology of Spinal Anesthesia, Second edition. Baltimore, Williams & Wilkins, 1969
3. Reitan JA, Tengert KB, Wymore ML, et al: Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 57:31-36, 1978

---

## Scavenging of Anesthetic Gases

To the Editor:

We would like to comment on the editorial by Miller and Cullen[1] which considered the question of whether scavenging is worth the cost.

In discussing the most recent case of near fatality produced by operational failure of a scavenger system,[2] they listed the disadvantages of routine scavenging. Among them: (A) The high cost of installation of scavenging devices. (B) Scavenging systems encourage continued reliance on recirculating air conditioning systems because of the high energy demands of non-recirculating systems. Recirculating air conditioning systems employ high-efficiency particulate air filters which do not, however, remove anesthetic vapors and gases. (C) The potential injuries to patients when one more device is attached to anesthetic machines as an "afterthought" instead of being part of the original design. (D) The questionable methodology used in the various reports incriminating the pollution of operating rooms by anesthetic gases as a possible cause of a putative increased incidence of hepatic disease, miscarriages, teratogenicity and cancer thought to occur in personnel working in this area.

The fact is that the validity of most studies indicating that pollution of operating room air by trace concentrations of anesthetics constitutes a hazard to operating room personnel is open to question. Most of these studies have been conducted by mail questionnaires with little or no direct verification. At the time the editorial was written the most objective study investigating the incidence of cancer or liver disease among anesthetists,[3] in which results were obtained from autopsies and death certificates, fails to substantiate the theory that the incidence of cancer and liver disease is greater among anesthetists than among other physicians. The paper by Ericson and Kaller,[4] appearing in the same issue as the editorial, objectively investigated the frequency of abortion and congenital abnormalities in the offspring of 494 women who worked in operating rooms during their pregnancies. It, too, found no difference between the study group and a control group. Finally, Lew,[5] an epidemiology consultant for the American Cancer Society, in an examination of death certificates of 610 anesthesiologists who died between 1954 and 1976 found no indication of an increased rate of deaths due to cancer or hepatic or renal disease among male anesthetists.

The exposure limits in the standards initially proposed by NIOSH for operating room air were 25 ppm for $N_2O$ and 1 ppm of halothane or enflurane.[6] There is, however, no conclusive evidence that even 100 ppm of $N_2O$ or 4 ppm of halothane is actually dangerous under clinical conditions. What is the rationale for these specific limits?

Perhaps the lack of objective evidence has been the reason why OSHA (the acting branch of the US Department of Health, Education, and Welfare) has thus far failed to implement the standards recommended by NIOSH more than 2 years ago.[5]

If one is concerned about the operating room pollution, a viable and effective alternative to scavengers is use of low flows and closed systems for anesthesia. This reduces and nearly abolishes operating room pollution, saves the costs of scavenging systems, eliminates the risks associated with their use, and avoids the need for monitoring anesthetic gases and for having the air conditioning apparatus changed. Without scavenging, nitrous oxide concentrations inhaled by operating room personnel were shown by Virtue et al[7] to be below the proposed standards when low flow or closed systems were used. Low flow techniques are becoming more and more popular, but for those reluctant to adopt them, the alternative is the use of scavengers, with all the potential dangers pointed out by Miller and Cullen.

J. Antonio Aldrete, MD
Robert W. Virtue, MD, PhD
*Department of Anesthesiology*
*University of Colorado Medical School*
*Denver, Colorado 80262*

REFERENCES

1. Miller MG, Cullen BF: The cost of scavenging: Is it worth it? Anesth Analg 58:265-266, 1979
2. Patel KD, Dalal FY: A potential hazard of the Dräger scavenging interface for wall suction. Anesth Analg 58:327-328, 1979
3. Doll R, Peter R: Mortality among doctors in different occupations. Br Med J 1:1433-1435, 1977

4. Ericson A, Källen B: Survey of infants born in 1973 or 1975 to Swedish women working in operating rooms during their pregnancies. Anesth Analg 58:302–305, 1979
5. Lew EA: Mortality experience among anesthesiologists, 1954–1976. Anesthesiology 51: 195–199, 1979
6. Criteria for a recommended standard ... occupational exposure to waste anesthetic gases and vapors. US Department of Health, Education and Welfare. Publication #77-140, PHS Center for Disease Control, NIOSH, 1977
7. Virtue RW, Escobar A, Modell JG: Nitrous oxide levels in operating room air with various gas flows. Can Anaesth Soc J 26:313–318, 1979

---

## Anesthesia for Aortocoronary Bypass Surgery

Between 1964 and 1978, aortocoronary bypass graft procedures were performed in more than 300,000 patients. The procedure itself can result in perioperative myocardial infarction. Such infarcts have been demonstrated in 7 to 46% of patients by electrocardiographic changes, and use of enzymes, while radioactive nucleotide imaging raises the percentage even higher. Greater understanding of and constant attention to the myocardial oxygen ($O_2$) supply and demand may reduce the incidence of perioperative myocardial infarction. Some of the factors influencing supply and demand can be controlled pharmacologically. Drugs such as nitroglycerin, nitroprusside, and propranolol can reduce the myocardial $O_2$ demand. Unfortunately, there are few data to elucidate the relationship between myocardial $O_2$ demand and supply as influenced by anesthetic drugs, especially in patients with myocardial ischemia. Recent developments in anesthetic management afford better means for protection of the ischemic myocardium during and after operation. (*Tarhan S, White RD, Raimundo HS: Anesthetic considerations for aortocoronary bypass graft surgery* (*Review Article*). *Ann Thorac Surg 27:376–389, 1979*)

# book REVIEWS

## Principles and Practice of Blood-Gas Analysis, by A. P. Adams and C. E. W. Hahn, London, Franklin Scientific Products, Ltd, 1979, 95 pp.

This excellent little book presents a lucid account of the basic principles of blood gas analysis and their clinical interpretation. A clinician's investment of the couple of evenings or a weekend required to read this book will be well spent. This is especially so since the authors have a happy knack of explaining, illustrating, and giving examples of difficult concepts in an easy to understand and perhaps slightly different manner than that found in the standard anesthesiology textbook chapters on the subject. This serves to reinforce the pleasure in reading this monograph and increases one's comprehension of the subject matter.

The initial chapters explain the physical and chemical laws governing gas behavior and explore acid-base balance and the physiology of oxygen and carbon dioxide, including their transport by blood. There follows a valuable chapter on the clinical interpretation of blood gases and acid-base problems. The next two chapters discuss the working principles of the $P_{O_2}$, $P_{CO_2}$, and pH electrodes and the quality control that must be used to obtain an accurate measurement with them. A further chapter analyzes the correction factors that should be made to account for the patient's temperature and the time between sampling and making a measurement. Oxygen content and hemoglobin saturation measurements are then described. The final chapter reviews the current status of in vivo and transcutaneous blood gas analysis.

Peter A. Southorn, MD
Assistant Professor of
Anesthesiology
Mayo Medical School
Rochester, MN

## Advances in Pain Research and Therapy, by J. J. Bonica, J. C. Liebeskind, and D. G. Albe-Fessard, New York, Raven Press, 1979, 984 pp, $75.00.

This volume contains the selected papers presented at the Second World Congress on Pain held in 1978 in Montreal, Canada.

In the initial chapter, Professor Manfred Zimmerman presents an excellent discussion on "Neurophysiology of Nociception." His lecture was exceptionally well received, delivered with up-to-date data and theory, and organized in the best association between basic research and clinical problems.

Later chapters discuss the topics: Pain Related to Peripheral Nerve Lesions; Orofacial and Head Pain; Endogenous Mechanisms of Pain Inhibition; Low Back Pain; Measurement of Pain in Man and Animals; and Other Pain Researches and Therapies. The contributors on those topics, recognized as experts in their fields, succeed in providing authoritative and comprehensive materials on current progress.

Professor John J. Bonica, as he has done in the past, arranged the papers within each section in a scientifically logical sequence, and succeeds in promoting the dissemination of new information, and stimulating greater research efforts. He has undertaken enormous effort to promote the cause of improving the care of patients suffering from pain.

This volume will be of great interest to biomedical researchers and health professionals, and it should be a welcomed addition to all those who are involved in pain diagnosis and pain therapy.

Josef K. Wang, MD
Assistant Professor of
Anesthesia
Mayo Medical School
Rochester, MN

## The Recovery Room, by C. B. Drain and S. B. Shipley, Philadelphia, W. B. Saunders Co, 1979, 608 pp, $16.95.

In this text the authors attempt to better correlate the nursing literature regarding recovery room care and the postanesthesia requirements as seen from the anesthetist's viewpoint. It is their intent that the total patient care experience in the postanesthesia recovery room be more complete and more related to the patient's anesthesia and surgical requirements.

Drain and Shipley's approach to this goal has been to present their material in five sections. Section I, The Recovery Room as a Separate Unit, describes the physical plant and essential equipment that distinguishes a postanesthesia recovery room from other areas of the hospital, defines the staffing problems and requirements, and briefly discusses certain administrative and management considerations. Section II, Physiologic Considerations in the Recovery Room, is intended to highlight the critical aspects of recovery room care. This includes a review of the anatomy and physiology of major body systems with an attempt to illustrate for the recovery room nurses the many clinical problems they face in the care of the postsurgical and postanesthesia patient whose care demands that they understand well the anatomic facts and physiologic principles involved. Section III, Concepts in Anesthetic Agents, is a review of anesthetic agents and techniques with particular attention to their effects in the immediate postanesthesia period. Section IV, Post-operative Nursing Care in the Recovery Room, includes approximately 300 pages and provides a discussion of nursing care considerations following surgery to various body systems. Chapters in this section are divided according to specialty care areas, ie, neurosurgery, orthopedic surgery, thoracic surgery, etc. The chapters in Section V, Special Considerations, discuss specific medical conditions or physical states which the authors feel require a specific knowledge and skill in the individual recovery room practitioner to enable the provision of the best nursing care in these unique situations. The individualized areas of special consideration include among others, the geriatric patient, the pediatric patient, shock, and cardiopulmonary resuscitation.

Although the depth of coverage of material varies among the five sections, the coverage is reasonably well balanced in the chapters within each particular section. Reviews of anatomy and physiology must necessarily be somewhat sketchy where they are presented as an introduction to better understanding of postsurgical and postanesthesia problems. The authors make liberal use of familiar illustrations from standard textbooks which complement graphically their written discussion. Each chapter offers short introductory paragraphs which are useful to the reader in that they suggest the content of the succeeding topics for discussion and attempt to relate the chapter's content to those postanesthesia or postsurgical clinical situations where the recovery room nurse has an important role to play.

The section on anesthetic agents serves as an adequate introduction for nonanesthesia personnel. Descriptions of anesthetic agents are brief and the more recent studies relating to metabolism and toxicity are not discussed. The discussion of muscle relaxants and reversal techniques could be improved upon as could certain word phrases such as post-tetanic "fasciculation" and the spelling of certain drugs. The sentence referring to patients receiving topical anesthesia of an extremity in the conduction anesthesia section and a suggestion that motor weakness remains for as long as 18 hours following intravenous regional anesthesia with bupivacaine further limit the usefulness of this material for instruction of anesthesia personnel. The large section dedicated to postoperative care after particular types of surgery is instructional and is well written. There is a particularly lengthy and informative chapter on postoperative care following neurosurgery.

At least one basic approach to patient care is presented as a useful guideline for the beginning recovery room nurse. It is not intended that this material be accepted by all as the only care plan to be followed. Additions and modification of the recommendations made in this text are commonplace in many of our recovery rooms today. Nevertheless, the material presented serves a most useful purpose in preparing the recovery room nurse to meet the nursing care challenges presented by the patients of the various surgical specialties. Illustrations in this section are simple, adequate in number, and assist the reader in understanding the material presented in the text; rarely are they mislabeled or have legend incomplete. The references following each chapter though not as numerous as in preceding sections of the book, still include several up-to-date sources.

This book was written primarily for beginning recovery room nurses and can be recommended as a study text to provide useful guidelines in their professional development. It was not intended to be, and does not serve as, a useful text in the clinical training of anesthesia personnel. It would be of interest, however, for all practitioners of anesthesia who are involved in the responsibilities of developing and maintaining high levels of nursing care practices in the post-anesthesia recovery room. It can be a useful guide in planning a continuing medical education program with the recovery room nursing staff.

Richard R. Ritter, MD
Brooke Army Medical Center
San Antonio, TX

---

## Pediatric Respiratory Therapy, Second Edition, by M. D. Lough, C. F. Doershuk, and R. C. Stern, Chicago, Year Book Medical Publishers, 1979, 313 pp, $18.95.

In the first edition of this book a group of dedicated professionals drawing on long years of clinical experience gave birth to a text which covered a wide range of basic pediatric pulmonary issues. The intended audience—postgraduate health personnel including respiratory therapists, physical therapists, nurses, and physicians—read, enjoyed, benefited, and endorsed its value. The book served to fill a void for those making the transition from student to respiratory care provider.

This edition represents a limited expansion of the Case Western-Rainbow Babies and Children's Hospital approach to respiratory problems. It fails to reflect the exciting adaptations of respiratory technology to pathophysiology that have occurred in pediatric intensive care units throughout North America. There is minimal discussion of intermittent-mandatory-ventilation, nuances of end-expiratory pressure systems, Swan-Ganz catheters, and noninvasive oxygen and carbon dioxide analysis. The authors do not offer concepts important to the application of respiratory support technology for children with head injuries, pulmonary hypertension, bronchopulmonary dysplasia, burns, and chronic neuromuscular disease. With the exception of cystic fibrosis, pediatric pulmonary diseases are covered in a cursory manner. Diseases are described as phenomena requiring specific treatment. Natural history multisystem effects, variations of pathophysiology, and the need to titrate support and therapy are understated or ignored. For those who want to interface technology with disordered physiologic systems, to achieve a result beneficial to the patient, this text offers little help.

Anesthesiologists and pediatric intensivists may find the book useful as a refresher of certain fundamentals—lung development, defense and regulatory mechanisms, and pulmonary function. Also, the chapter on care of equipment is of some practical value. Here management dogma is more important than the concept of titration of therapy, and the details of cleaning, sterilization, and decontamination are appropriately presented.

Overall, this may be a useful reference for respiratory therapists and technicians who occasionally deal with the pediatric patient. However, for those actively dealing with pediatric pulmonary problems, it is not sufficiently current to recommend purchase.

Robert G. Kettrick, MD
Assistant Professor of
Anesthesiology
University of Pennsylvania
School of Medicine
Associate Director, PICU
Children's Hospital of
Philadelphia
Philadelphia, PA

### **Manual of Pediatric Anesthesia,** edited by D. J. Steward, New York, Churchill Livingstone, 1979, 305 pp, $15.95.

The Department of Anesthesia at The Hospital for Sick Children (HSC), Toronto, Canada, is world-renowned for its excellence in pediatric anesthesia and intensive care. The authors present a concisely written text that fulfills three general aims: "first, to discuss the *important* differences in anatomy and physiology of children compared with adults; second, to present the general principles of anesthetic management of pediatric patients; and third, to describe techniques of anesthesia used in HSC for some specific procedures."

The manual is divided into three parts. The first part provides the foundations for pediatric anesthesia by describing the peculiarities of pediatric anatomy, physiology, pharmacology, and psychology. General guidelines for anesthesia also are provided in this section of the manual. In addition, the management of some systemic disorders with anesthetic implications are discussed in considerable detail. The second part of the manual deals with anesthesia for specific procedures, discussed in the following format: (1) a short paragraph describing the syndrome including associated conditions, (2) pertinent details of surgical procedures, (3) special anesthetic problems, (4) anesthetic management (divided into preoperative, perioperative, and postoperative sections), and (5) suggested additional reading with key articles noted. The third part of the book is an appendix divided into five sections: (a) an excellent table of syndromes with a succinct description of the syndrome and discussion of the anesthetic implications of a syndrome, (b) an outline of suggested minimal length of time a patient should be kept in a recovery room, (c) an outline of the usual drug dosages in pediatric anesthesia (which needs a little expansion), (d) pediatric cardiopulmonary resuscitation, and (e) a list of manufacturers and suppliers of pediatric anesthesia equipment. In addition, there is a complete and thorough index.

Overall, this manual is excellent. Although there are other ways of managing many of the patients described, one cannot go wrong by following the techniques employed by the Department of Anesthesia of HSC who give more than 14,000 anesthetics a year. Many succinct "rules of thumb" are provided. This manual is really an HSC anesthesia resident's manual, and is somewhat institutional in its approach and rather dogmatic in several areas. There is also some unnecessary redundancy in the various chapters which could be eliminated by better editing; at the same time, recapitulation of prior incidental discussions of a syndrome would be helpful if also included in the main discussion of the management of the syndrome. Because of its clinical orientation, I strongly recommend this book to every anesthesia resident and as part of the library of any practitioner who occasionally administers anesthesia to infants and children.

Eugene K. Betts, MD
Assistant Anesthesiologist and
Assistant Professor of Anesthesia
The Children's Hospital
of Philadelphia
Philadelphia, PA

## BOOK NOTE

### **Seminars in Respiratory Medicine,** edited by T. L. Petty and R. M. Cherniack, New York, Stratton Intercontinental Medical Book Corporation, July, 1979, 98 pp, published quarterly, $28.00/year.

This quarterly publication has the stated aim of providing the clinician with up-to-date information about the treatment of respiratory disease more rapidly and frequently than textbook or monograph. The July 1979 issue (Volume 1, Number 1) deals with chronic respiratory insufficiency, and each future issue will apparently deal with a specific entity.

## BOOKS RECEIVED

**Dental Anesthesia and Analgesia,** by G. D. Allen. Baltimore, Williams & Wilkins, 1979, 446 pp, $24.95.

**Der alte Mensch in der Chirurgie,** by J. H. Rehn. Berlin, Springer-Verlag KG, 1979, 245 pp.

**Outpatient Surgery,** by R. C. Schultz. Philadelphia, Lea & Febiger, 1979, 470 pp, $48.50.

**Acute Care,** edited by B. M. Tavares and R. Frey. Secaucus, NJ, Springer-Verlag, 1979, 345 pp, $42.90.

**Practical Mathematics in Allied Health,** by M. Waterhouse. Baltimore, Urban & Schwarzenberg, 1979, 243 pp, $15.95.

# A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

## Editorial Policies

Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

**Types of materials.** The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

**Peer review.** All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

**Legal and ethical considerations.** Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

**Editing.** All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

## Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

**Title Page.** The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

**Abstract and Key Words.** The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Define all abbreviations except those approved by the International System of Units.

*Key (indexing) terms.* Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract.

**Text.** The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

*Introduction.* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods.* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

*Results.* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

*Discussion.* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**References.** (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus.* Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus.* Consult the "List of Journals Indexed," printed annually in the January issue of *Index Medicus.*

Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

*Journal*

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

*Books and Other Monographs*

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

**Tables.** Type each table on a separate sheet: remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

**Illustrations.** Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of *original* drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 12.7 by 17.3 cm (5 by 7 in) but no larger than 20.3 by 25.4 cm (8 by 10 in). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them using paper clips. Do not bend figures.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with background.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, *regardless of authorship or publisher,* except for documents in the public domain.

For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Some journals publish illustrations in color only if the author pays for the extra cost.

**Legends for Illustrations.** Type legends for illustrations double spaced, starting on a separate page with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

**Abbreviations.** Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

**Cook County Graduate School of Medicine**

announces

**SPECIALTY REVIEW COURSE IN ANESTHESIOLOGY**

**May 11–16, 1980**

Alon P. Winnie, M.D., *Course Coordinator*
Chairman, Department of Anesthesia
Abraham Lincoln School of Medicine
University of Illinois

A six-day intensive review course which examines, in-depth, the clinical practice of Anesthesiology and the fundamental principles upon which it is based.

*A.M.A. Category I Credit: 54 Hours*

For further information and registration contact:

**Cook County Graduate School of Medicine**
**707 South Wood Street, Chicago, Illinois 60612**
**(312) 733-2800**

---

# *I.A.R.S. 1979*
# *REVIEW COURSES*

Booklet containing 14 Review Course Lectures given at 53rd Congress in March of 1979 is available from I.A.R.S. Cleveland business office at $5.00 per copy. Supply is limited and orders will be filled on basis of receipt date of order. Make checks payable to International Anesthesia Research Society and send with order.

……

I.A.R.S.
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Enclosed is check for $_____ for _____ copy(ies) of "1979 Review Course Lectures" to be sent to:

(name)

(Mail address)

(City-state-zip)

STATE UNIVERSITY
of
NEW YORK

Upstate
Medical
Center

## STAFF ANESTHESIOLOGIST

Two positions at the rank of Assistant or Associate Professor will be available after January 1, 1980. Responsibilities include teaching, at the undergraduate, graduate and postgraduate levels, research and service. Four years of postgraduate training and eligibility for a New York license is required. An interest in regional anesthesia, pain therapy or intensive care advantageous, but not essential. Highly competitive salary structure and excellent fringe benefits.

*Send curriculum vitae to:*

Howard L. Zauder, M.D., Ph.D.
Professor and Chairman
Department of Anesthesiology
State University of New York
Upstate Medical Center
Syracuse, New York 13210

## CLINICAL FACULTY POSITIONS OPEN
## 1980-1981
## COLLEGE OF MEDICINE, KING FAISAL UNIVERSITY DAMMAM, SAUDI ARABIA

The expanding College of Medicine at King Faisal University is going into its sixth year of development and invites applications from qualified clinical faculty for the 1980-1981 academic year in:

***ANESTHESIOLOGY***

SALARIES are highly competitive and negotiable; comparable to other Saudi universities.

BENEFITS include free furnished housing, educational allowances, air tickets to and from Saudi Arabia once each year for a family of four, 60-day paid vacation in the summer, liberal overweight allowance.

Contracts are for one year and are renewable. Language of instruction is English.

Send *curriculum vitae* with current telephone number, and the names and addresses of three references to:

DR. TAWFIQ TAMIMI
Dean, College of Medicine
King Faisal University

c/o Saudi Arabian
Educational Mission
2221 West Loop South
Houston, Texas 77027

P. O. Box 2
Sunbury-on-Thames
Middlesex
England TW16 5JP

*coming up next........*

## I.A.R.S. - 54th Congress

MGM GRAND HOTEL

RENO, NEVADA

March 9-13, 1980

## Anesthesia Symposium in Israel
### *"New Concepts of Old Problems"*

Nov. 6-14, 1980

Sponsored by the Department of Anesthesiology of Beth Israel Medical Center

***in affiliation with***

The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY)

**Speakers:** J. Kaplan, S. J. Thomas, J. Cottrell, H. Turndorf, S. Cotev, I. Azar, M. Finster, P. Poppers

**Topics:** Anesthetic Management of
1. Cardiac Patients
2. Increased Intracranial Pressure
3. High Risk Pregnancy

CME CAT. I-12 credit hours

**Information:** I. Azar, M.D.
Dept. of Anesthesiology
Beth Israel Medical Center
10 Nathan D. Perlman Place
New York, N.Y. 10003
Phone: (212) 420-2385

# classified ADVERTISING

**ANESTHESIOLOGIST—**

70-physician multispecialty group in Western Kentucky, expanding to 80 plus physicians and surgeons; excellent opening in section of four M.D. anesthesiologists and nine C.R.N.A.'s; new 401-bed hospital opening December 1979; early partnership with incentive income distribution formula. Subspecialty interest in cardiovascular surgery and conductive anesthesia desirable but not mandatory. Contact: Medical Director, Trover Clinic, Madisonville, Kentucky 42431: 502-821-7171, Extension 205.

**PENNSYLVANIA:**

Fellowship in Ob-Gyn Anesthesia. Designed to develop anesthesiology staff for maternity hospitals. Emphasis on conduction anesthesia techniques. In-depth training, clinical and teaching experience with investigative opportunities and maintenance of general anesthesia skills in gynecology, general surgery and dental surgery. Credited by the University of Pittsburgh, an equal opportunity/affirmative action employer. Pennsylvania license required. Appointment for six months or one year. Contact: R. McKenzie, MD, FFARCS (Eng.), Director of Anesthesia, Magee-Womens Hospital, Pittsburgh, PA 15213.

**ILLINOIS:**

Immediate openings for Board Certified/Eligible Anesthesiologists—Assistant and Associate Professors. Research Opportunities. Applications with Curriculum Vitae should be forwarded to: Dr. Donald Benson, University of Chicago, Department of Anesthesiology, 950 E. 59th Street, Chicago, Ill. 60637. AN EQUAL OPPORTUNITY EMPLOYER.

**ANESTHESIOLOGIST:**

FMG Board Eligible. Has Flex. Available 1980, April. Trained in University Hospitals. Experienced in all kinds of anesthesia. Will consider all locations. Reply to Box 2-80-B, c/o IARS.

**ANESTHESIOLOGIST:**

Board certified with four years of real life clinical experience, familiar with critical care medicine, able to organize and upgrade a department's activities, current in all areas of anesthesia including cardiac, neuro and pediatrics, is seeking a private practice of anesthesia involving primarily supervision and teaching but also direct patient care and departmental function, in a growing community and a hospital with great potential. Send information to Box 11-79-A, c/o I.A.R.S.

**MAYO FOUNDATION, DEPARTMENT OF ANESTHESIOLOGY—**

Opportunities for advanced subspecialty training in cardiovascular and neuro-anesthesia, respiratory intensive care, and pain management are available to qualified candidates. Indepth training experience in one or more of these areas for periods of six months to two years may be arranged. For additional details, contact: Alan D. Sessler, M.D., Chairman, Department of Anesthesiology, Mayo Foundation, Rochester, Minnesota 55901.

**WEST VIRGINIA:**

Pain Clinic Fellowship commencing July 1, 1980 available to applicant with three years post graduate training in anesthesiology. Multi-disciplined Pain Clinic, seeing approximately 2,000 patients yearly, 25% of which are new patients. Clinic based on out-patient model with in-house beds available. Regular staff includes three anesthesiologists, a psychiatrist, and two clinical psychologists. Ancillary services include physical therapy, oral surgery and family practice. For further information contact Robert Bettinger, M.D., Director of Pain Clinic, Department of Anesthesiology, West Virginia University Medical Center, Morgantown, West Virginia 26506. Deadline for applications is April 1, 1980. An equal opportunity/affirmative action employer.

**PEDIATRIC ANESTHESIOLOGY RESIDENCY**

Childrens Hospital of Los Angeles has advanced clinical program for residents at the second and third year level of training. Also accepting applications from practicing anesthesiologists who wish to update their knowledge and proficiency. Positions available from 2 months to 1 year. Specialized year approved by the AMA. For further details contact:

George B. Lewis, Jr., MD
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, CA 90027
Phone (213) 662-1708

**NEW YORK:**

Residencies in Anesthesiology at New York University Medical Center: University Hospital, Bellevue Hospital Center and New York Veterans Administration Hospital. Applications invited for training at all levels. Particular emphasis is placed on the use of monitoring techniques in critically ill and traumatized patients. Specialized year opportunities exist in Cardiac Anesthesia, Neurosurgical Anesthesia, Obstetrical Anesthesia, Pediatric Anesthesia and Research. For further information write to Herman Turndorf, M.D., Professor and Chairman, Department of Anesthesiology, New York University Medical Center, 550 First Avenue, New York, N.Y. 10016.

**ANESTHESIOLOGY RESIDENCY TRAINING PROGRAM**

Opening in January 1980 for PGY-2 or 3. Program approved for specialized years in Neurosurgical, Pediatric, and Cardiac Anesthesia, Research, Critical Care and Pain Management. Over 10,000 anesthetic procedures yearly! Exciting metropolitan area, with unusual educational, cultural, and sporting opportunities. Write Patricia S. Underwood, M.D., Anesthesia Training Program, Montefiore Hospital, Department of Anesthesiology, 111 East 210th Street, Bronx, NY 100467.

# classified ADVERTISING

### RESIDENTS—ANESTHESIOLOGY.

New Jersey Medical School, an affiliated hospital, Anesthesiology residency positions. 3 years approved program. Please direct all inquiries to: Dr. Wen H. Wu, Professor & Chairman, Dept. of Anesthesiology, Medical Science Bldg., Rm. E538, or call (201) 456-5119. COLLEGE OF MEDICINE & DENTISTRY OF NEW JERSEY—New Jersey Medical School, 100 Bergen St., Newark, NJ 07103. Equal Opportunity/Affirmative Action Employer M/F.

### TEXAS:

Board-certified or board-eligible anesthesiologist wanted to join department consisting of 2 board-certified anesthesiologists and 3 hospital employed CRNAs in 392-bed acute care hospital. Caseload consists primarily of general surgery, gynecology, minimal OB coverage, orthopedics and no cardiac surgery. Fee-for-service practice with generous first year salary guarantee. Texas malpractice rates are minimal and there is no state income tax. Our city has 170,500 people, low housing and utility costs, and a very modern medical center. For further details write to Box 2-80-D, c/o I.A.R.S.

### ANESTHESIOLOGIST

Needed Now! Boards—Group Practice—Fee/Service Full time—Phoenix, Arizona Area. Please send CV to Box 2-80-A, c/o IARS.

### OBSTETRIC ANESTHESIA:

Approved one-year specialty training at high-risk obstetrical unit—3,000 deliveries per year. Ample opportunity for clinical experience, teaching, clinical and animal research using chronic maternal-fetal sheep preparation. Available July 1, 1980. Contact: John B. Craft, Jr., M.D., Director, OB Anesthesia, George Washington University Hospital, 901 23rd St. NW, Washington, D.C. 20037—(202) 676-3864. An Equal Opportunity, Affirmative Action Employer.

### ANESTHESIOLOGIST

Position available for an Anesthesiologist in an active 460-bed general medical and surgical teaching hospital with strong affiliation with University of Missouri Medical School. Prefer candidate who is board certified or eligible. Licensure in any of the 50 states acceptable. Salary range $40,000 to $50,112 per year dependent on qualifications plus handsome bonus. Liberal fringe benefits. Call or write Warren P. Sights, M.D., Acting Chief of Staff, Harry S. Truman Memorial Veterans Hospital, 800 Stadium Road, Columbia, MO 65201, phone (314) 443-2511 ext. 6010. An Equal Opportunity Employer.

### ANESTHESIOLOGIST

Needed in small Minnesota city. Challenging cases, no open heart. Malpractice insurance paid. Salary first year, then buy-in. Reply to Box 9-79-H, c/o I.A.R.S.

### ACADEMIC ANESTHESIOLOGIST, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE.

Position for eligible or board certified anesthesiologist with rank commensurate with qualifications. Duties include patient care, medical student and resident teaching, and research. Specific interests may include any subspecialty. Must be eligible for licensure in Kentucky. Inquiry from all qualified applicants welcome. Competitive salary and fringe benefits. Send inquiry, curriculum vitae, and names of four references to George E. Webb, M.D., Chairman, Department of Anesthesiology, P. O. Box 35260, Louisville, Kentucky 40232. An equal opportunity, affirmative action employer.

### ANESTHESIOLOGIST

wishes to relocate. 37, Board certified, FMG, five years of clinical experiences. Available in July, 1980. Reply to Box 2-80-C, c/o I.A.R.S.

*Rates for classified advertising: $3.00 per line, minimum 5 lines; box number ads $3.50 per line. Classified display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia, 3645 Warrensville Center Rd., Cleveland, OH 44122.*

# INDEX OF ADVERTISERS

American Optical—*AO® Flexible Laryngoscope* . . . . Cover 3

Arrow International, Inc.—*Central Vein Catheterization Kit* . . . . (21)

Arrow International, Inc.—*Percutaneous Sheath Introducer* . . . . (7)

Ayerst Laboratories—*Fluothane®* . . . . (14), (15), (16)

Beth Israel Medical Center—*Anesthesia Symposium* . . . . (31)

Breon Laboratories Inc.—*Marcaine* . . . . (24), (25)

Bristol Laboratories (Division of Bristol-Myers Co.)—*Stadol* . . . . (4), (5), (6)

Chemetron Medical Products—*Anesthesia Machine* . . . . Cover 4

Cook County Graduate School of Medicine—*Symposium* . . . . (30)

Critikon, Inc.—*Corporate Introduction* . . . . (17), (18), (19), (20)

Endo Laboratories—*Narcan®* . . . . (10), (11), (12)

King Faisal University—*Employment Opportunity* . . . . (31)

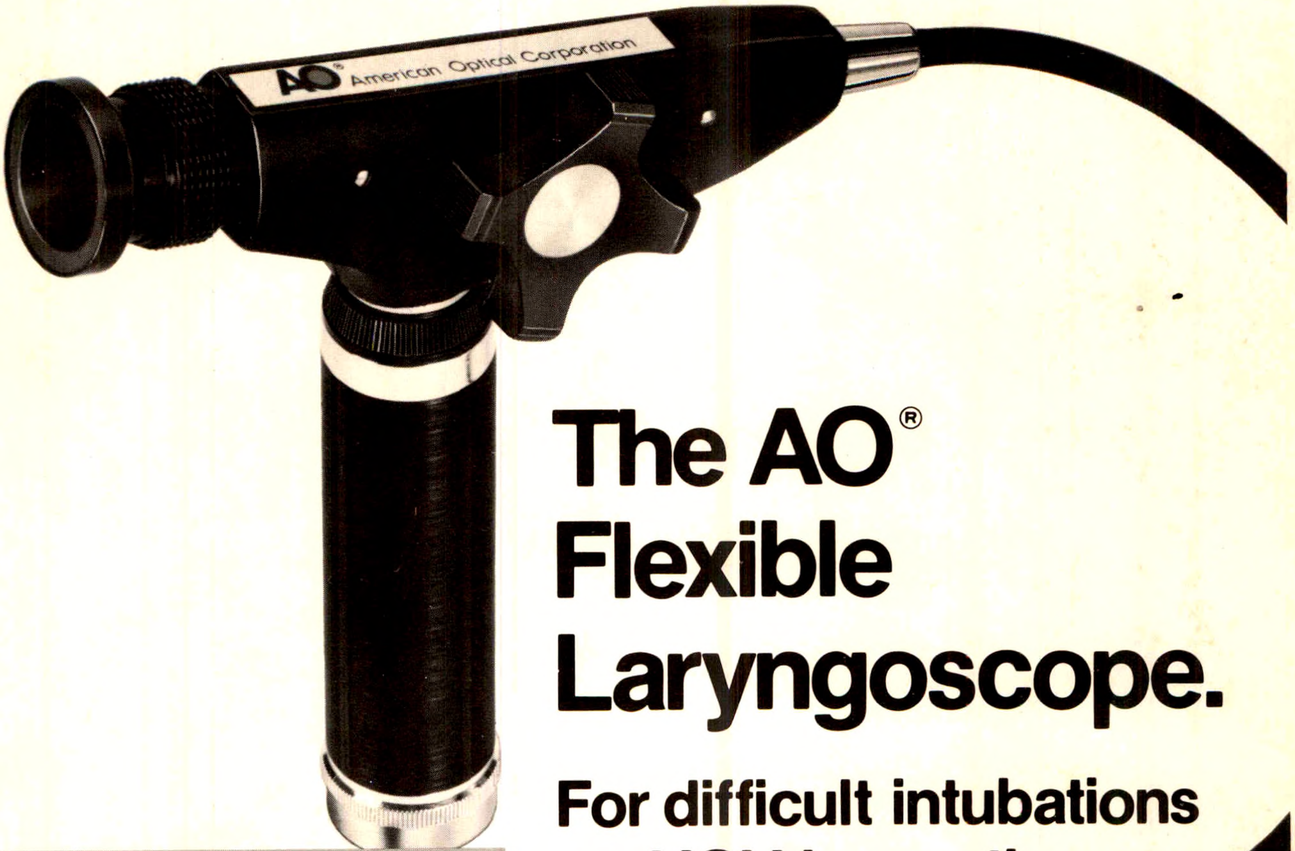
La Barge, Inc.—*Surgical Temperature Monitoring System* . . . . Cover 2

Parke-Davis—*Ketalar®* . . . . (8), (9)

Physio-Control Corporation—*Lifepak 6* . . . . (13)

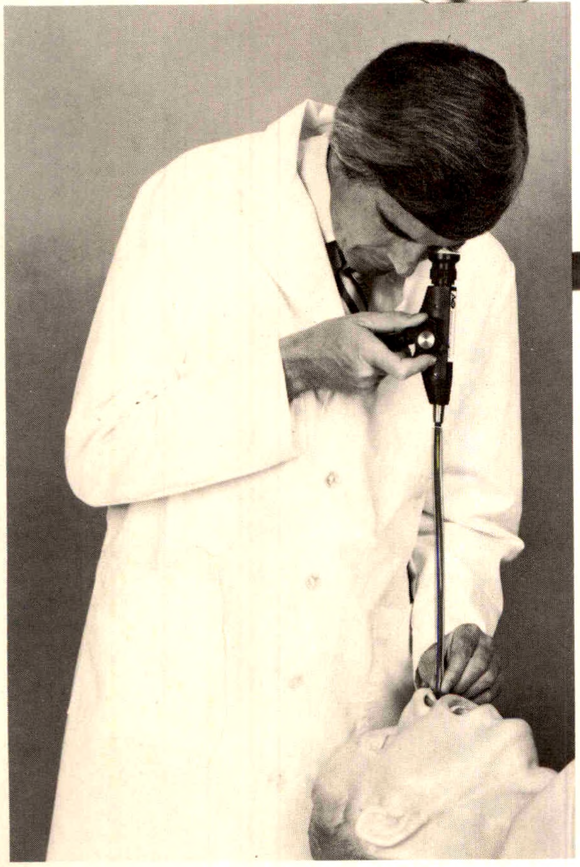
Siemens/Elema AB—*Servo Ventilator System* . . . . (22), (23)

State University of New York—*Employment Opportunity* . . . . (31)



# The AO® Flexible Laryngoscope.

## For difficult intubations and ICU inspections.



The AO Flexible Laryngoscope facilitates difficult intubations, minimizes trauma and aides proper tube placement.

- Illuminates internal anatomy.
- Gives direct, clear view of path.
- Remote control guides tip around obstructions.
- Withdraws easily when tube is in place.
- Bright, built-in light source, completely portable.
- For both nasal and oral introduction.

For complete details contact American Optical, Scientific Instrument Division, Southbridge, MA 01550 or phone (617) 765-9711, Ext. 2445.

AO®
American
Optical

# Can your anesthesia machine pass Chemetron's four-point safety test?

Pass Fail
☐ ☐ **Does it help prevent internal gas line hookup to the wrong gas service?**
Chemetron's inhalation anesthesia machine comes with specially engineered fittings that are coded for each gas. This helps you eliminate the chance for a gas line to be hooked up to the wrong gas. That means increased safety.

Pass Fail
☐ ☐ **Does it eliminate the problem of vaporizers contaminating one another?**
Chemetron's anesthesia machine has parallel vaporizer mounts. Since they're not in series, they help keep anesthetic agent vapors from contaminating other vaporizers.

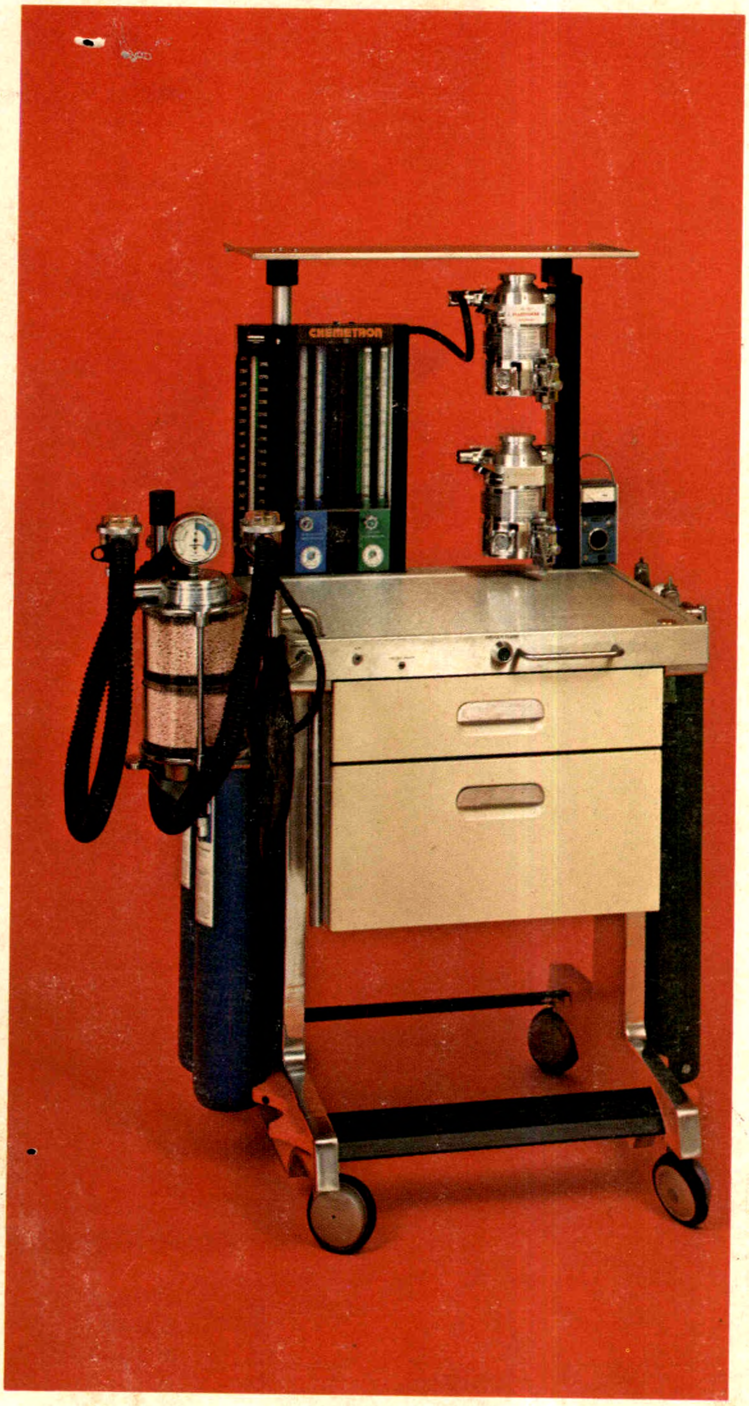
Pass Fail
☐ ☐ **Is it designed so that a flow meter tube cannot be placed in the wrong position?**
Chemetron has a safety keying system for the individual flow meter tubes. Because each tube is calibrated differently, each base is designed differently and will not accept the wrong tube. So the danger of measuring a gas flow with the wrong calibration is reduced.

Pass Fail
☐ ☐ **Is the oxygen flow control knob touch-coded?**
Chemetron's is. The oxygen valve has a scalloped edge, the others a smooth one. So you can rely on your fingers, as well as your eyes, to help you achieve maximum safety.

**Get instantaneous respiratory and anesthetic gas analysis, too.**
Introducing the Chemetron Medspect II system. A compact, mobile, mass spectrometer that analyzes inspired and expired levels of $O_2$, $CO_2$, $N_2$, $N_2O$ and either halothane or ethrane during anesthesia delivery. Simultaneously. Instantaneously. Noninvasively.

**To get the full report, call (800) 325-3890.**
To find out more about the Chemetron anesthesia machine, call Randy Olson toll-free at (800) 325-3890. (He'll also direct you to your nearest Chemetron distributor.) For the whole story on Medspect II, call Judy Snyderman at (301) 944-4020. Or write Chemetron Medical Products, 1801 Lilly Ave., St. Louis, MO 63110.

**CHEMETRON® Medical Products**
Chemetron Corporation. A member company of Allegheny Ludlum Industries, Inc.



ISSN 0003-2999
vol. 59, no. 3 March 1980

Acc.
29.7.80

# Anesthesia and Analgesia

**Journal of the International Anesthesia Research Society**

OLDEST PUBLICATION IN THE SPECIALTY–
ESTABLISHED 1922

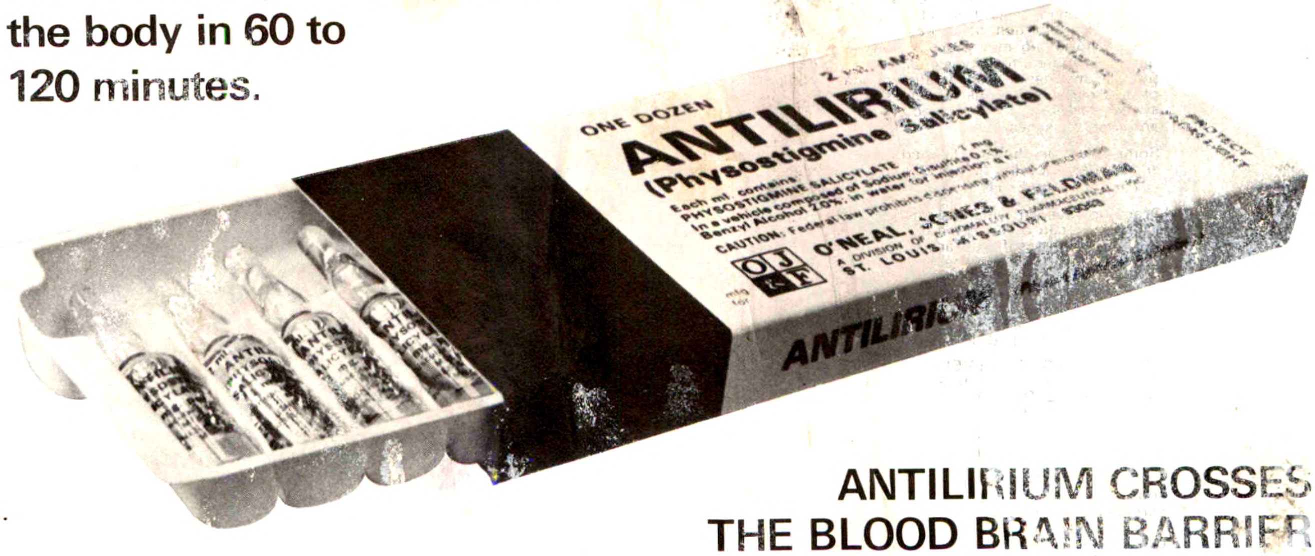
# ANTILIRIUM

## (Physostigmine Salicylate)

**QUICKLY BECOMING THE DRUG OF CHOICE FOR REVERSING PROLONGED SOMNOLENCE, DELIRIUM AND OTHER ANTICHOLINERGIC SIDE EFFECTS.**

More Anesthesiologists are relying on ANTILIRIUM because...

- Patients are revived in minutes after I.V. administration.
- Reverses anticholinergic side effects.
- Patient safety—metabolized in the body in 60 to 120 minutes.


ONE DOZEN
2 ml. AMPULES
ANTILIRIUM
(Physostigmine Salicylate)
Each ml. contains:
PHYSOSTIGMINE SALICYLATE 1 mg
CAUTION: Federal law prohibits dispensing without prescription
O'NEAL, JONES & FELDMAN
ST. LOUIS, MISSOURI
OJ&F
ANTILIRIUM

ANTILIRIUM CROSSES THE BLOOD BRAIN BARRIER WHEREAS NEOSTIGMINE DOES NOT

ANTILIRIUM, unlike other anticholinesterases including neostigmine does not have a quaternary nitrogen atom, but has a tertiary amine. For this reason it is nonionized and rapidly crosses the blood brain barrier.

OJ&F O'NEAL, JONES & FELDMAN PHARMACEUTICALS • ST. LOUIS, MO 63043

# ANTILIRIUM

## (Physostigmine Salicylate)

**DESCRIPTION**: ANTILIRIUM Injection (physostigmine salicylate) is OJF's brand of physostigmine salicylate.

ANTILIRIUM INJECTION 1 mg./ml.
FOR INTRAMUSCULAR OR INTRAVENOUS USE
Each ml. contains:
PHYSOSTIGMINE SALICYLATE 1 mg.
In a vehicle composed of Sodium Bisulfite 0.1%, Benzyl Alcohol 2.0%; in water for injection q.s.

**ACTION**: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. The action of acetylcholine is normally very fleeting because of its hydrolysis by a specific enzyme. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine. The changes in body function which are produced by the injection of physostigmine are, therefore, very similar to those which would occur from simultaneous stimulation of the parasympathetic nerves and include contraction of the pupil, increased tonus of the intestinal musculature, constriction of the bronchi and stimulation of secretion of the salivary and sweat glands.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quarternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Drugs with anticholinergic properties primarily antagonize acetylcholine competitively at the neuroreceptor site. Cardiac muscle, exocrine glands, and smooth muscle are most markedly affected. Action of the inhibitors is overcome by increasing the level of acetylcholine naturally generated in the body through inhibiting the enzyme (cholinesterase) which normally prevents accumulation of excess acetylcholine. It does this by hydrolyzing that compound to inactive acetic acid and choline. Agents which inhibit this enzyme, so that acetylcholine accumulates at the neuroreceptor site are called anticholinesterases.

Physostigmine, one of the anticholine esterases which is a tertiary amine, crosses into the central nervous system and can reverse both central and peripheral anticholinergic actions.

The anticholinergic syndrome has both central and peripheral signs and symptoms. Central toxic effects include anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Severe poisoning may produce coma, medullary paralysis, and death. Peripheral toxicity is characterized by tachycardia, hyperpyrexia, mydriasis, vasodilatation, urinary retention, diminution of gastrointestinal motility, decrease of secretion in salivary and sweat glands, and loss of secretions in the pharynx, bronchi, and nasal passages.

Some drugs in the anticholinergic group, such as imipramine and related tricyclics also produce additional toxic effects such as cardiac arrhythmias which can be reversed by physostigmine.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Toxic effects from mixed drug ingestions and combination preparations such as amitriptyline and perphenazine may respond less dramatically. Since physostigmine is rapidly metabolized, therapeutic doses may be necessary at intervals as life-threatening signs such as arrhythmias, convulsions, and deep coma recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

**INDICATIONS**: **TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.**

It has also been reported that ANTILIRIUM (physostigmine salicylate) may antagonize the CNS depressant effects of diazepam.

**CONTRAINDICATIONS**: Physostigmine salicylate injections should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents (decamethonium, succinylcholine).

**WARNING**: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions. An overdosage of ANTILIRIUM can cause a cholinergic crisis.

**PRECAUTIONS**: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is antagonist and antidote for physostigmine.

**ADMINISTRATION AND DOSAGE**: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur. Physostigmine salicylate is rapidly metabolized in the body.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: Ampuls, 2 ml. packed 12 per box.

**O'NEAL, JONES & FELDMAN**
ST. LOUIS, MISSOURI 63043

1079

# I.A.R.S. 1979 REVIEW COURSES

Booklet containing 14 Review Course Lectures given at 53rd Congress in March of 1979 is available from I.A.R.S. Cleveland business office at $5.00 per copy. Supply is limited and orders will be filled on basis of receipt date of order. Make checks payable to International Anesthesia Research Society and send with order.

........................................................................

I.A.R.S.
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Enclosed is check for $________ for ________ copy(ies) of "1979 Review Course Lectures" to be sent to:

__________________________________
(name)

__________________________________
(Mail address)

__________________________________
(City-state-zip)

OF MEDICINE LIBRARY UNIVERSITY

# Today's First Choice

# Ethrane® (enflurane)

## Anesthetists are now using Ethrane (enflurane) more often than any other potent anesthetic.

## *Their reasons?*

- **Stability of heart rhythm**
  A noteworthy feature of anesthesia with Ethrane (enflurane) is stability of heart rhythm[1].
- **Compatibility with epinephrine**
  The compatibility of Ethrane (enflurane) with epinephrine used for hemostasis is such that up to 10 ml of 1:100,000 or 1:200,000 epinephrine solution may be injected subcutaneously over a 10 minute period. Up to 30 ml of epinephrine solution may be administered over the period of an hour.
- **Minimal or no liver changes**
  Ethrane (enflurane) has produced either no change or small, transient increases in liver enzymes. Repeated enflurane anesthesias also have not significantly altered these values[2–6].
- **Minute-by-minute control**
  With a blood/gas partition coefficient of only 1.9, Ethrane (enflurane) provides for a rapid induction and for rapid changes in depth to meet varying needs of surgery and patient management.
- **Potentiation of nondepolarizing relaxants**
  Clinical use suggests that ½ to ⅓ the usual dose of nondepolarizing relaxant is required when anesthesia is combined with enflurane. This potentiating effect helps reduce the risk of residual or recurring postanesthetic paralysis.
- **Rapid recovery; minimal anesthetic after-effect**
  Because of enflurane's low solubility in blood, patients emerge from anesthesia promptly with little or no depression of mental function or residual symptomatic effect.

1. Dobkin AB, Nishioka K, Gengaje DB, et al: Ethrane (compound 347) anesthesia: a clinical and laboratory review of 700 cases. Anesth Analg 48:477-493, 1969.
2. Botty C, Brown B, Stanley V, et al: Clinical experiences with compound 347, a halogenated anesthetic agent. Anesth Analg 47:499-505, 1968.
3. Lebowitz MH, Blitt CD, Dillon JB: Clinical investigation of compound 347 (Ethrane). Anesth Analg 49:1-10, 1970.
4. Linde HW, Lamb VE, Quimby CW, et al: The search for better anesthetic agents: Clinical investigation of Ethrane. Anesthesiology 32:555-559, 1970.
5. Virtue RW, Lund LO, Phelps JR, et al: Difluormethyl 1,1,2-trifluoro-2-chloroethyl ether as an anesthetic agent: results with dogs and a preliminary note on observations with man. Canad Anaesth Soc J 13:233-241, 1966.
6. Allen PJ, Downing JW: A prospective study of hepatocellular function after repeated exposure to halothane or enflurane in women undergoing radium therapy for cervical cancer. Brit J. Anaesth 49:1035-1039, 1977.
7. Hanquet M: Enflurane (Ethrane) anesthesia. A survey of the first 1000 cases. Acta Anaesthesiol Belg 25:289-299, 1974.

Ethrane (enflurane)
Today's First Choice

Ohio Medical Products
3030 Airco Drive
Madison, Wisconsin 53707

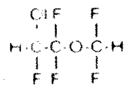
AIRCO®

# Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

## DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$\mathrm{H{-}CClF{-}CF_2{-}O{-}CF_2{-}H}$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \qquad A = 7.967 \quad B = -1678.4 \quad T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

## ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High $pCO_2$ levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

## INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

## CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

## WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

## PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. [illegible]ucose elevation should be considered in diabetic patients. [illegible]NE (enflurane) should be used with caution in patients w[illegible]rtue of medical or drug history could be considered m[illegible]ible to cortical stimulation produced by this drug. As [illegible] general anesthetics and some muscle relaxants, hyp[illegible]as been observed with the use of ETHRANE.

## ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

## DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

**Induction:** Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

**Maintenance:** Surgical levels of anesthesia may be obtained with 1.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

**Overdosage:** In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

## PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Products
Division of Airco Inc.
P.O. Box 7550, 3030 Airco Drive, Madison, Wis. 5370

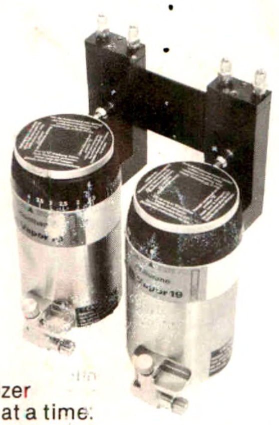
AIRCO®

# NEW from NORTH AMERICAN DRÄGER

North American Drager is continually keeping in touch with the growing needs of the anesthesia profession. We are constantly improving our products for patient safety, our prime engineering and design criterion. These new products join the ever growing range of North American Drager Products of Anesthesia.

**DPM 2**
**(DRAGER PRESSURE MONITOR II)**

Our second generation of pressure monitors.
Four pressure monitors—minimum ventilation pressure, continuing pressure, high pressure and sub atmosphere pressure.

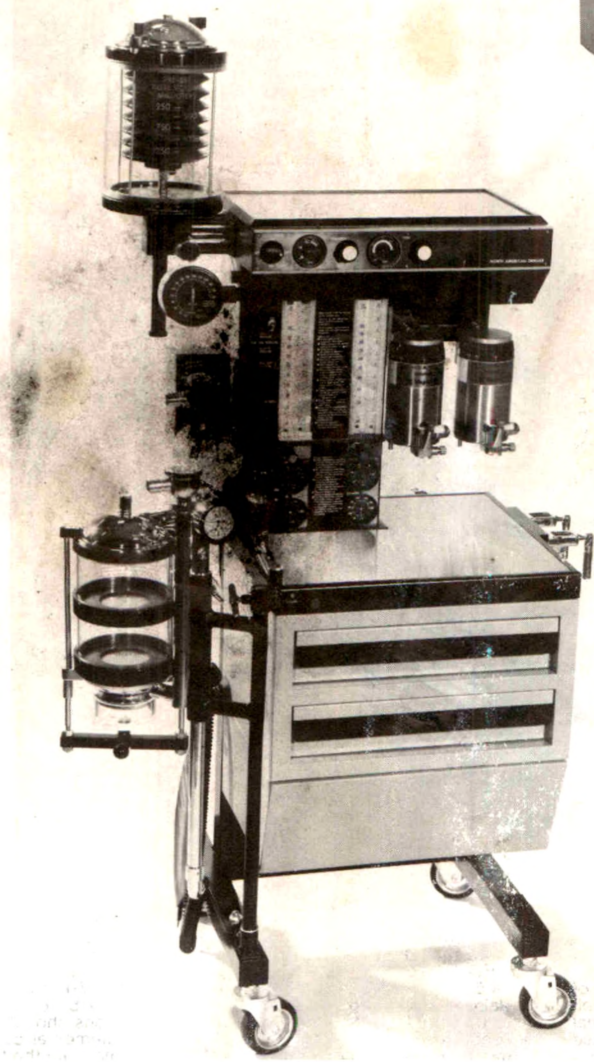


**VAPORIZER EXCLUSION SYSTEM**

A unique lock out system for insuring that only one vaporizer can be switched on at a time.

**PHILLIPS LARYNGOSCOPE BLADE**

Combines the features of the Miller Blade and the Jackson-Eversole Blade. Now in Two Sizes—Adult and Pediatric.



**NARKOMED 2 ANESTHESIA SYSTEM**

The newest member of the North American Drager family of Anesthesia Systems.
A complete anesthesia system consisting of an anesthesia dispensing system, ventilation system, patient monitoring system and a unique patient safety alarm system.

NORTH NA AMERICAN DRÄGER
148B QUARRY ROAD TELFORD, PENNSYLVANIA 18969

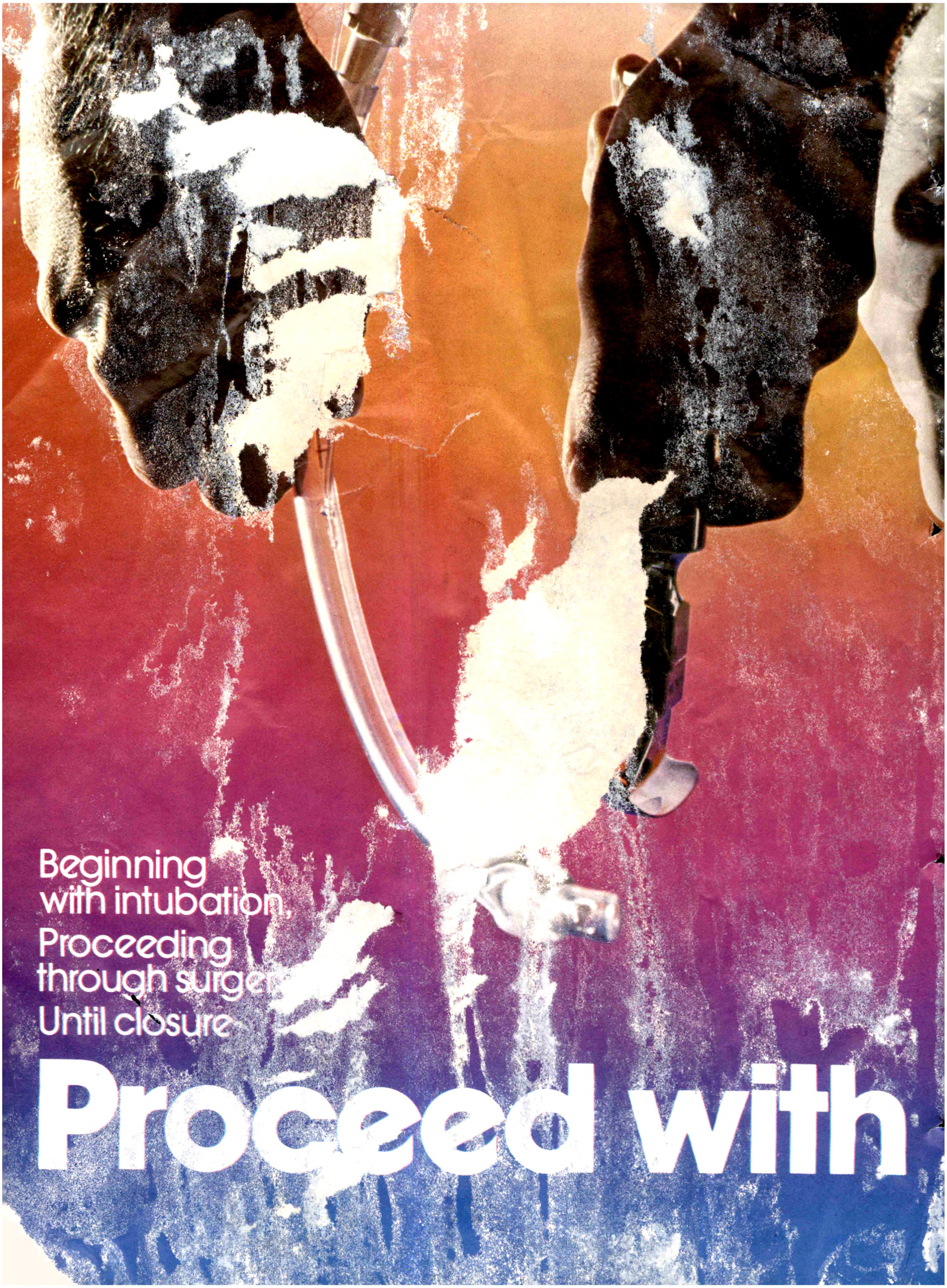
NORTH NA AMERICAN DRÄGER
148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969

☐ Please send Anesthesia Accessories catalog

☐ Please have N.A.D. representative call

☐ Please include information on Anesthesia Machines

NAME ____________________
DEPARTMENT ____________________
HOSPITAL ____________________
ADDRESS ____________________
CITY ____________________ STATE ______ ZIP ______
TELEPHONE ____________________


Beginning
with intubation,
Proceeding
through surgery
Until closure
Proceed with

Pavulon facilitates intubation and provide safe neuromuscular blockade.

Histamine release and ganglionic blockade are rarely, if ever, seen[1]

Organon

[illegible] PART OF [illegible]ZONA INC

O[illegible] Pharmaceuticals
[illegible] of Organon Inc.
[illegible] N.J. 07052

# PAVULON

pancuronium bromide

For a brief summary of prescribing information, please see the following page

Until closure
**Proceed with PAVULON®**
pancuronium bromide
The clinically proven nondepolarizing muscle relaxant

**Brief Summary** (Please consult full package insert, enclosed in every package, before using Pavulon).

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

**CAUTION:** Federal law prohibits dispensing without prescription.

**Reference:**
1. Stanley and Liu. Anesth Analg 56 669, 1977

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

## ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA, effective

______________________________

**From**—(Current or former address)

______________________________

Street Address

______________________________

City, State, Zip Code

**Important: Show your name and address exactly as your Journal is now addressed.**

______________________________

To—(New Address)

______________________________

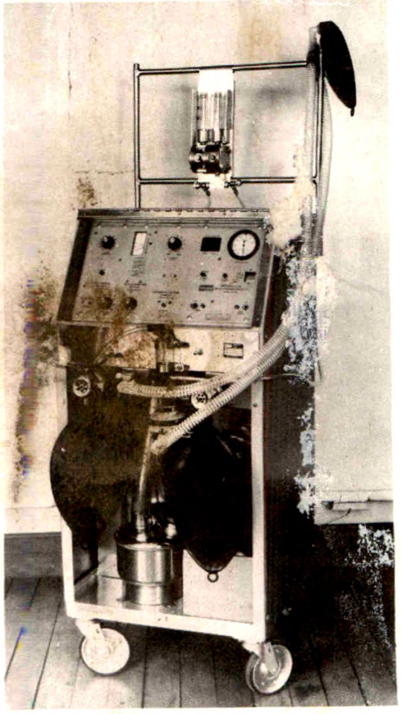
Street Address

______________________________

City, State, Zip Code

______________________________

Print Your Name



**EMERSON**

**IMV Ventilator**

*Intermittent Mandatory Ventilation*

Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all –– and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of $CO_2$ rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV

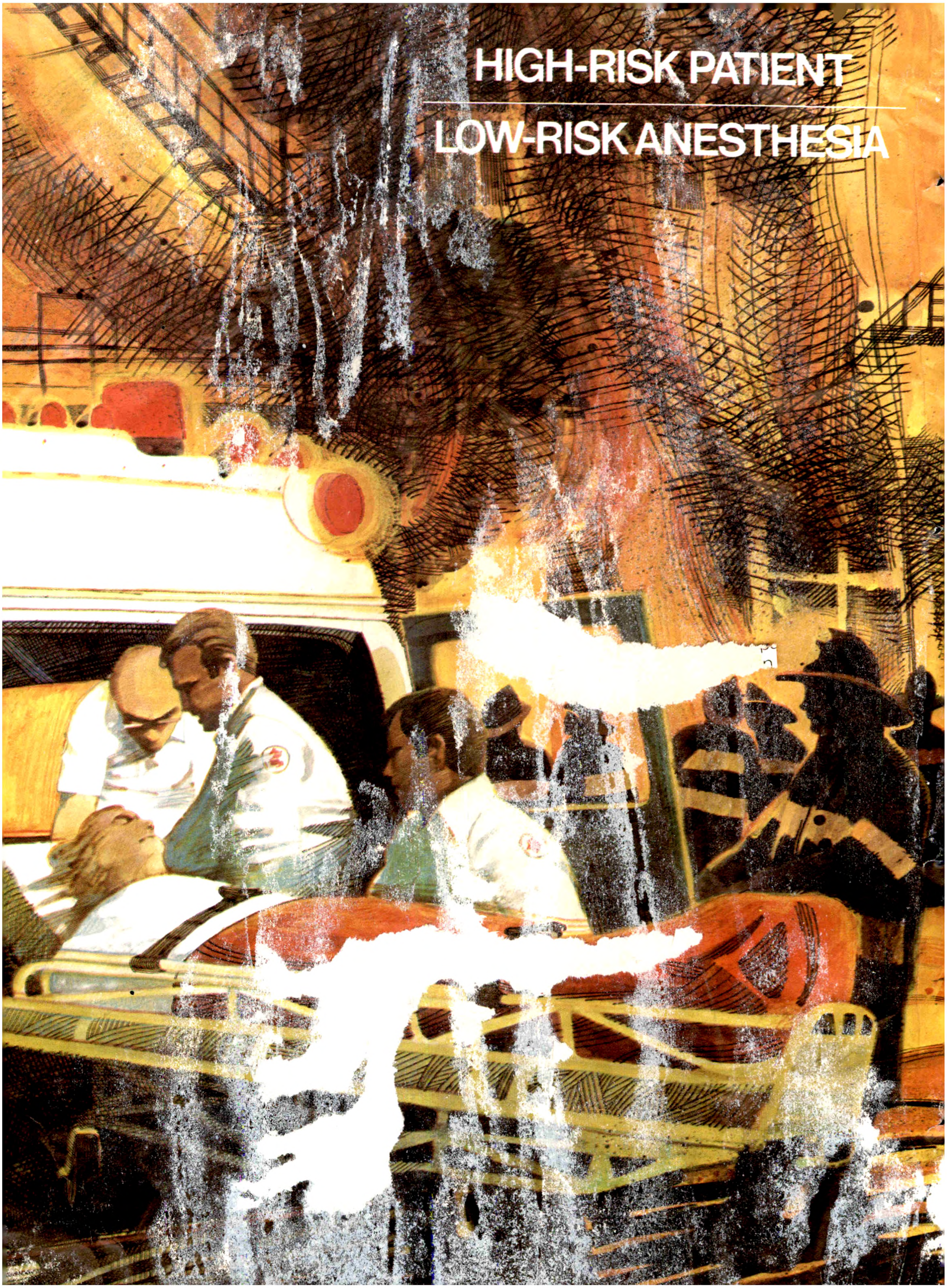
*Please request Form 3-MV.*

**J. H. EMERSON COMPANY**

**CAMBRIDGE, MASSACHUSETTS 02140**

# HIGH-RISK PATIENT

# LOW-RISK ANESTHESIA



# Ketalar®

## (ketamine hydrochloride injection, NF)

### Features you need...

Smooth, rapid onset of anesthesia, profound analgesia, IM or IV administration. Little risk of liver damage or buildup of tolerance following repeated procedures. Ketalar usually strengthens, rather than depresses, blood pressure, pulse rate and respiration. When necessary, it permits maintenance of unaided respiration because of minimal relaxation of skeletal muscles or laryngeal-pharyngeal reflexes.

### for the patients who need them

At either end of the age spectrum, the pediatric or geriatric patient. The patient in shock, or with shock potential. Patients in whom establishing an IV route of administration is difficult. The burn patient requiring repeated dressing changes. Patients requiring manipulative or diagnostic proc[illegible]
The debilitated patient. The emergenc[illegible]
may not have a[illegible]

BRIEF SUMMARY OF PRESCRIBING INFORMATION

**SPECIAL NOTE**

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA-SHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

**CONTRAINDICATIONS**

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

**WARNINGS**

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

5. Postoperative confusional states may occur during the recovery period.

6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

***Usage in Pregnancy:*** Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

**PRECAUTIONS**

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

2. Resuscitative equipment should be ready for use.

3. **The incidence of emergence reactions may be reduced** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

**ADVERSE REACTIONS**

*Cardiovascular:* Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

*Respiration:* Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway [illegible] tion have occurred during Ketalar anesthesia.

[illegible] Diplopia and nystagmus have been noted following Ketalar administration. [illegible] may cause a slight elevation in intraocular pressure measurement.

[illegible] *[illegible]logical:* (See Special Note)

[illegible] ome patients enhanced skeletal muscle tone may be manifested [illegible] ents sometim[illegible] resembling seizures (see Dosage and [illegible]

[illegible] ng [illegible] miting have been observed; however this [illegible] us [illegible] ility of patients to take liquids by [illegible] h sho [illegible] (see Dosage and Administration). [illegible] neral: [illegible] thema at the injection site have infrequently been [illegible] ted. Tra[illegible] d/or m[illegible] rash have also been reported.

**[illegible] SUPPL[illegible]**

[illegible] lar is supp[illegible] loride [illegible] trations equivalent to ketamine [illegible] base.

[illegible] 0071-4581 [illegible] mg/ml. Supplied in cartons of 10.
[illegible] 0071-4581 [illegible] mg/ml. Supplied in cartons of 10.
[illegible] 0071-4582 [illegible] mg/ml. Supplied in cartons of 10.
[illegible] 0071-4585 [illegible] vial [illegible] mg/ml. Supplied in cartons of 10.

**SG**

**[illegible]ARKE-[illegible]**

[illegible] E-DAVIS
[illegible] n of Warner-Lambert Company
M[illegible] Plains, NJ 07950

PD-JA-2645-1-[illegible] ([illegible])

©1979 W[illegible] Lambert Company

# *Anesthesia and Analgesia*

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | 4 | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | 4 | 5 | 6 |
| 36 | 1957 | – | 2 | 3 | – | – | 6 | 44 | 1965 | – | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | 3 | 4 | 5 | 6 |
| 38 | 1959 | 1 | | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | 5 | 6 |
| 39 | 1960 | - | | 3 | 4 | 5 | 6 | 47 | 1968 | – | 2 | 3 | 4 | 5 | 6 |
| 40 | 1961 | | – | 3 | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | 4 | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | 2 | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | 3 | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 |
| 59 | 1980 | 1 | | | | | |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.
BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955
OTHER PUBLICATIONS AVAILABLE:
"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.
Ten-Year (1960-1969) Cumulative Index—$3.00.
Ten-Year (1970-1979) Cumulative Index—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd
Cleveland, Ohio 44122
Please send me the publications circled above, or listed hereunder:

☐ Check for $........ enclosed.
☐ Please send bill with understanding that ordered material will be sent when payment is received.
Name ..........................................
Address ..........................................
City, State, Zip ..........................................

## THERMODILUTION CARDIAC OUTPUT COMPUTER

**MODEL 3500E**

Latest bedside cardiac output computer monitoring technology

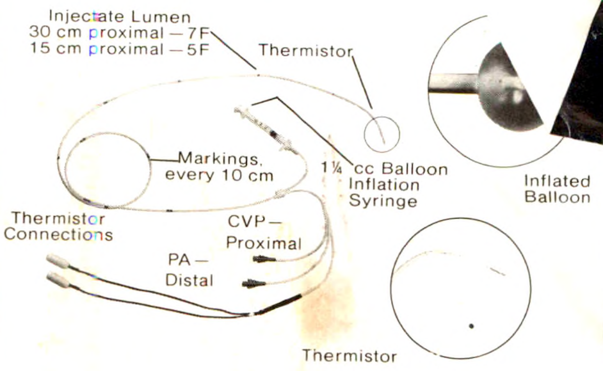
**MODEL 3501**

Companion automatic recorder for thermodilution curve.

**Features:**

- ACCURATE cardiac outputs — adult and pediatric ranges
- SIMPLE pushbutton operation
- ADJUSTABLE test calibration
- AUTOMATIC body and injectate temperatures
- AUTOMATIC thermal curve recording
- CHOICE of injectate volume and temperature
- SERVICEABLE — interchangeable circuitry

## THERMODILUTI
## CATHETERS



**Features:**

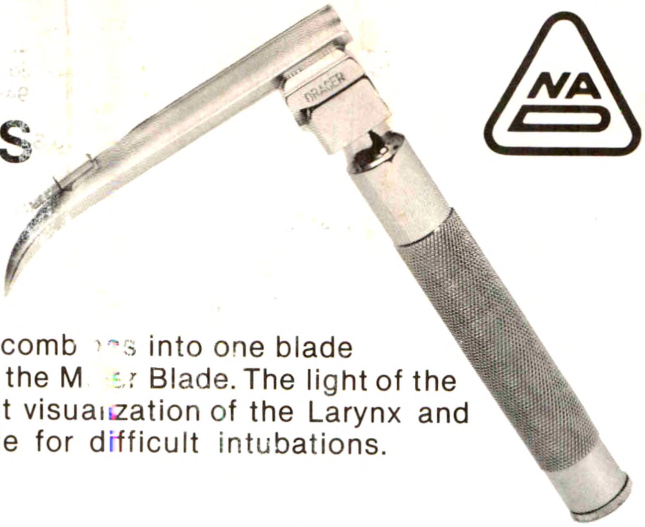
- Convenient and complete sterile packaging
- Precalibrated and interchangeable
- Adult, pediatric and direct placement sizes
- Ta[illegible]p — pressure fidelity ar[illegible]uction
- Th[illegible] located inside J cur[illegible]events P.A. wall contact
- Bal[illegible] protection shield

KMA INC

*For additional information contact Ross A. Linnemann*

**KIMRAY MEDICAL ASSOCIATES**
53 N.W. 42nd, Oklahoma City, Oklahoma 73118
(405) 525-3623

# PHILLIPS
## LARYNGOSCOPE BLADES
### Now Two Sizes
### Adult and Pediatric



The Phillips Blade by North American Drager combines into one blade many features of the Jackson-Eversole Blade and the M[illegible]r Blade. The light of the Phillips Blade is on the left side to afford excellent visualization of the Larynx and allows room for passing a tube along the blade for difficult intubations.

The Adult Blade has been found adequate for the largest adults encountered; the small tip, in addition makes it adaptable for use in children as small as 2 or 3 years of age. The Pediatric Blade is a replica of the Adult Blade that has been reduced in all aspects of shape and size, including thickness of the metal. It can be used in patients from newborn to about 4 years of age.

**NORTH AMERICAN DRAGER**
148B QUARRY ROAD, TELFORD, PA 18969

**Brief Summary of Prescribing Information**
**STADOL® (butorphanol tartrate)**

For complete information, consult Official Package Circular.

(2) 12/10/79

**INDICATIONS AND USAGE**—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

**CONTRAINDICATIONS**—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

**WARNINGS—Patients Physically Dependent on Narcotics:** Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

**Drug Dependence:** Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

**Head Injury and Increased Intracranial Pressure:** Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

**Cardiovascular Effects:** Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

**PRECAUTIONS—Certain Respiratory Conditions:** Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

**Impaired Renal or Hepatic Function:** Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such [illegible]. Extensive liver disease may predispose to greater side effects and grea[illegible] m the usual clinical dose, possibly the result of decreased meta[illegible] by the liver.

**Biliary Surgery:** Clinical studies have not [illegible] h the safety of Stadol administration to patients about to undergo [illegible] iliary tract.

**Usage as a Preoperative or Preanesthetic Medicati[illegible]:** Slight [illegible] ases in systolic blood pressure may occur, therefore caution should [illegible] employ [illegible] when Stadol is used in the hypertensive patient.

**Usage in Balanced Anesthesia:** The use of [illegible] ancuronium in combination with Stadol may cause an increase in conjunctival changes.

**Usage in Pregnancy:** The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been perfo[illegible] rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

**Usage in Labor and Delivery:** Safety to the mother and fetus following administration of Stadol during labor has been established. Pat[illegible] receiving Stadol during labor have experienced no adverse effects other than [illegible] with commonly used analgesics. Stadol should be used with caution in [illegible] re infants.

**Usage in Nursing Mothers:** The use of Stadol [illegible] infants is not recommended since it is [illegible] human milk. Stadol has been used safe[illegible] sequently nursed their infants.

**Usage in Children:** Safety and efficacy in children be[illegible] ars have not been established.

**ADVERSE REACTIONS**—The most frequent adverse reactions [illegible] 50 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy [illegible] (76, [illegible]). Less frequent reactions are: headache (35, 3%), vertigo (33, 3[illegible]), [illegible] 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lig[illegible]

Other adverse reactions which may occur (reported incidence of less than [illegible]%) a[illegible]

**CNS:** nervousness, unusual dreams, agitation, euphoria, hallucinations

**Autonomic:** flushing and warmth, dry mouth, sensitivity to cold

**Cardiovascular:** palpitation, increase or decrease of blood pressure

**Gastrointestinal:** vomiting

**Respiratory:** slowing of respiration, shallow breathing

**Dermatological:** rash or hives

**Eye:** diplopia or blurred vision

**OVERDOSAGE—Manifestations:** Although there have been no experiences of overdosage with Stadol during clinical trials, this may [illegible] due to accidental or intentional misuse as well as therapeutic use. Based [illegible] the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

**Treatment:** The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

**HOW SUPPLIED**—Stadol (butorphanol tartrate) injection for I.M. or I.V. use, is available as follows:

**NDC** 0015-5644-20—2 mg per ml, 2-ml vial
**NDC** 0015-5645-20—1 mg per ml, 1-ml vial
**NDC** 0015-5646-20—2 mg per ml, 1-ml vial
**NDC** 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
**NDC** 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

**BRISTOL**™

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

---

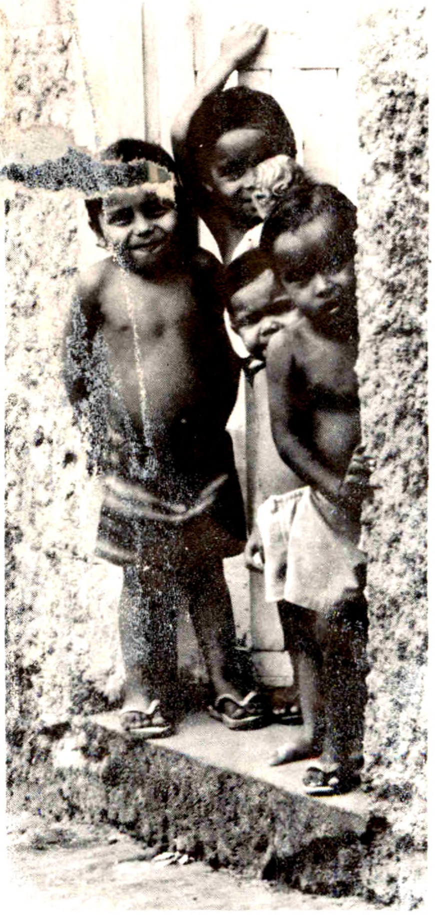
# Some doors are meant to be open...

Project HOPE is opening doors to children like these throughout the world. Since 1960 HOPE has sent teams of physicians, dentists, nurses and allied health personnel to share with developing nations their medical skills and knowledge.

Give to:

**PROJECT HOPE**

Department A
Washington, D.C. 20007



# The AO® Flexible Laryngoscope.

## For difficult intubations and ICU inspections.

The AO Flexi[illegible]scope facilitates difficult intub[illegible]trauma and aides proper tube placem[illegible]

- Illuminat[illegible]ial anatomy.
- Gives di[illegible]r view of path.
- Remote [illegible] guides tip around obstruct[illegible]
- Withdra[illegible]ly when tube is in place.
- Brigh[illegible]in light source, completely porta[illegible].
- For [illegible]h nasal and oral introduction.

For complete details contact American Optical, Scientific Instrument Division, Southbridge, MA 01550 or phone (617) 765-9711, Ext. 2445.

AO®
American
Optical

# CORTICOID THERAPY IN CRITICAL CARE

Pharmacologic doses of corticoids have been used in the treatment of shock unresponsive to conventional therapy, if adrenocortical insufficiency exists or is suspected.

## Differences That Count

Hexadrol® phosphate injection is easy to handle, store and administer. Already in solution, it can be used directly from the vial. Hexadrol has benzyl alcohol as a preservative and is stable at room temperature.

The multi-dose vial minimizes waste. When used in pharmacologic doses, Hexadrol offers significant savings over methylprednisolone.*

*Based on average wholesale price listings in Drug Topics Red Book 197[illegible]. Actual prices to direct purchasers will vary by order size but are usually lower for Hexadrol.

# Hexadrol® Phosphate Injection

## dexamethasone sodium phosphate injection USP

**BEFORE PRESCRIBING OR ADMINISTERING, PLEASE CONSULT COMPLETE PRODUCT INFORMATION, A SUMMARY OF WHICH FOLLOWS:**

**ACTIONS**—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

**CONTRAINDICATIONS**—Systemic fungal infections—Hypersensitivity to any component.

**WARNINGS**—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary fungal or viral ocular infections.

**Usage In Pregnancy.** Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

100 mg

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

**PRECAUTIONS**—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, apprOrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

**ADVERSE REACTIONS—**

**Fluid and electrolyte disturbances:** Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

**Musculoskeletal:** Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

**Gastrointestinal:** Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

**Dermatologic:** Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

**Neurological:** Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

**Endocrine:** Menstrual irregularities; Development of Cushingoid state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness. Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics.

**Ophthalmic:** Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

**Metabolic:** Negative nitrogen balance due to protein catabolism.

**Miscellaneous:** Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

**DOSAGE AND ADMINISTRATION**—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

**DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.**

**CAUTION**—Federal L[illegible]ts dispensing without prescription.

**HOW SUPPLIED**—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25; 10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

Hexadrol is available in two potencies, 4mg/cc and 10mg/cc in aqueous solution with 1% benzyl alcohol as preservative.

**When You Need it... Hexadrol Has It!**

Organon

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# THE WORLD IS ITS PROVING GROUND

**More widely investigated than any other inhalation anesthetic. Association with hepatotoxicity extremely rare.**[1]

Risk of liver toxicity from the use of FLUOTHANE® (halothane, U.S.P.) has been shown to be extremely rare. Unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and...the overall safety record of the anesthetic was excellent."[1]

These are conclusions drawn from the United States National Halothane Study, a comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE.

On the basis of postoperative morbidity for all types of operations, including high risk, the incidence for FLUOTHANE was 1.87%...compared with the 1.93% average for all anesthetic procedures.[2]*

**Over 450 million administrations worldwide.**

More anesthesiologists throughout the world choose FLUOTHANE more often than any other inhalation anesthetic. To date, there have been well over 110 million administrations in the United States alone... for a wide variety of procedures and techniques in patients of all ages.

**References:** 1. Brown, B.R., and Sipes, I.G.: Commentary-Biotransformation and hepatotoxicity of halothane. Biochem. Pharmacol. 26:2091, 1977. 2. Bunker, J.P., *et al:* The National Halothane Study, Washington, D.C. Government Printing Office, 1969.

## FLUOTHANE®

## (halothane, U.S.P.)

the most widely used inhalation anesthetic in the world

Ayerst

*See following page for full prescribing information

the most widely used inhalation anesthetic in the world

# FLUOTHANE®

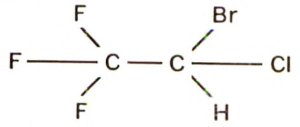
BRAND OF

# halothane, U.S.P.

for patients of any age, in almost any kind of surgery

*(Complete text of package circular.)*

**Description.** FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

**Actions.** FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE (halothane, U.S.P.) is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the [illegible] these changes be- [illegible] brady- [illegible] FLUOTH[illegible] e the release of ca[illegible] ergic stores. FLUOTH[illegible] of the ves[illegible] muscles.

Cardiac arrhyth[illegible] FLUOTHANE anesthesia. [illegible]al rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

**Indications.** FLUOTHANE is indicated for the induction and maintenance of general anesthesia.

**Contraindications.** FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

**Warnings.** When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, [illegible], particularly during assisted or controlled ventilation.

*Usage in Pregnancy.* Safe use of FLUOTHANE (halothane, U.S.P.) has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

**Precautions.** The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal [illegible] pressure. Therefore, in patients with [illegible] raised intracranial pressure, if [illegible] indicated, administration [illegible] d by measures ordinari- [illegible] cerebrospinal fluid pres- [illegible] be carefully assessed, an[illegible] to assist or control venti[illegible] oxygenation and ca[illegible].

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

**Adverse Reactions.** The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

**Dosage and Administration.** FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

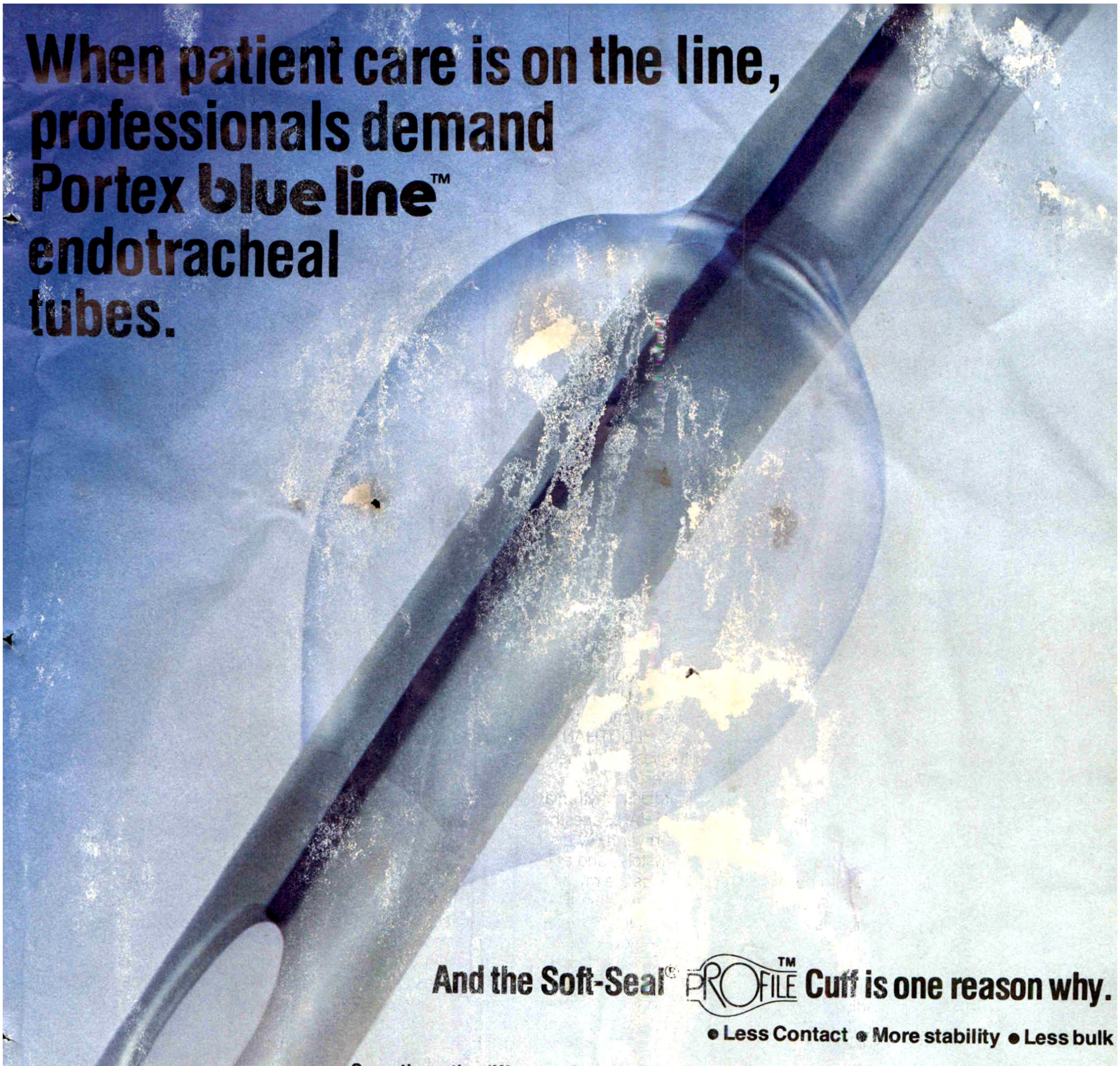
FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

**How Supplied.** No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w).

Ayerst.
Ayerst Laboratories
New York, N.Y. 10017

7918

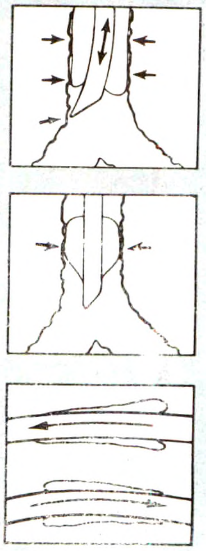
# When patient care is on the line, professionals demand Portex blue line™ endotracheal tubes.



## And the Soft-Seal® PROFILE™ Cuff is one reason why.

● Less Contact ● More stability ● Less bulk

**Sometimes the difference is the brand of endotracheal tube being used. That's why so many medical professionals put their trust in the Portex Soft-Seal Profile Cuff. It features high volume, low pressure and less bulk for easier intubation and extubation. The Profile Cuff. It's one more reason you should turn to Portex when caring is critical.**



- Larger area of old shape has much more contact with tracheal wall, thus more potential for tracheal wall irritation.
- Rectangular shape less stable, more possibility of undesirable movement of tube.

- New Profile shape greatly reduces area of contact with tracheal wall with less potential for tracheal wall irritation.
- Profile design offers greater stability, minimizes undesirable movement of tube, decreases possibility of "angling" of tip against sensitive tracheal wall.

- Less bulk when deflated. Streamline shape greatly aids intubation and extubation.

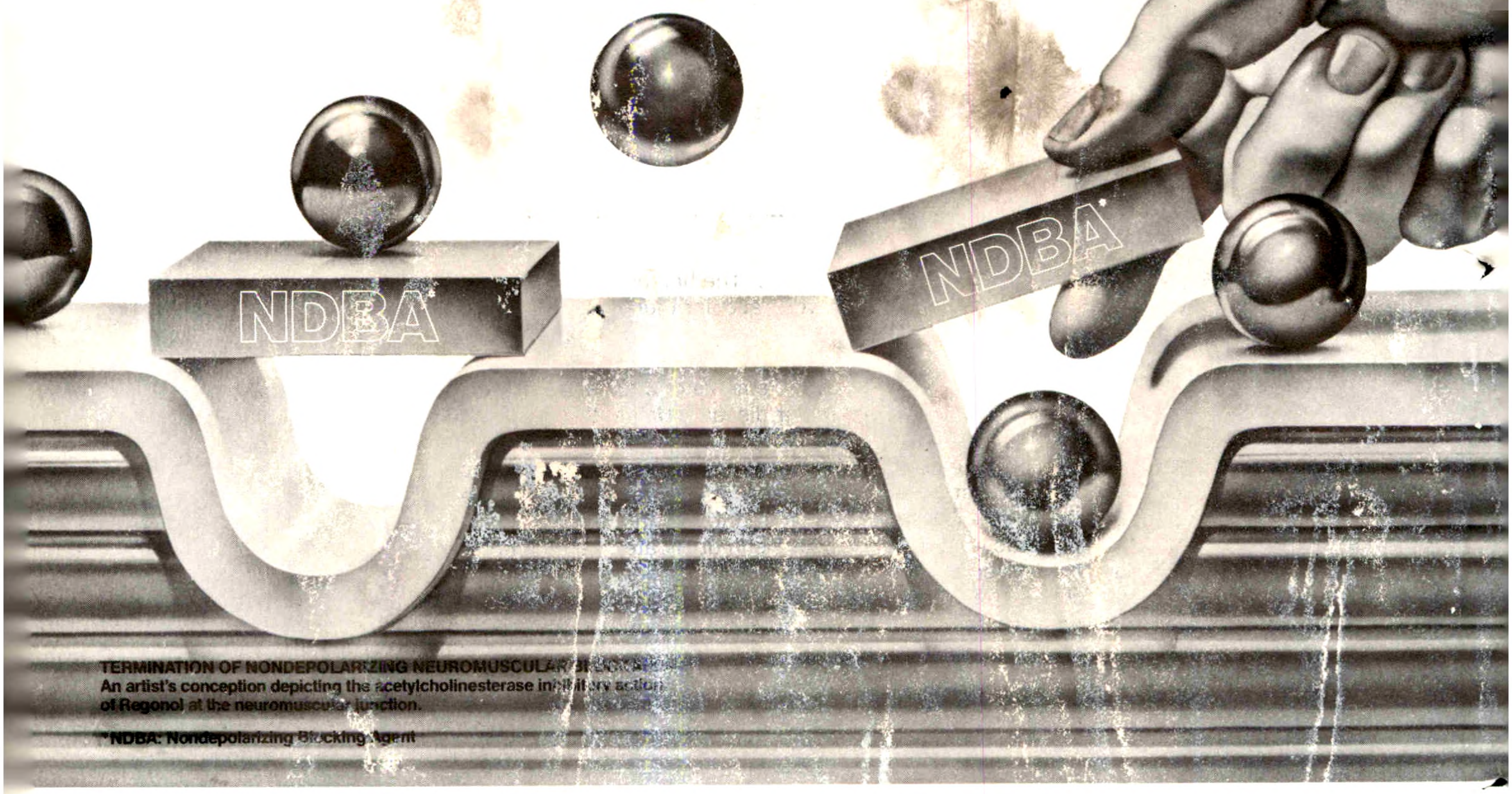
Portex, Inc. 42 Industrial Way, Wilmington, MA 01887 (617) 658-5110 In Ca [illegible] d Drive, Scarborough, Ontario

PORTEX®

Remove the Block Yourself

# Reverse with REGONOL® pyridostigmine bromide

Regonol rapidly restores full neuromuscular transmission. It produces fewer oropharyngeal secretions and less bradycardia than neostigmine.



**TERMINATION OF NONDEPOLARIZING NEUROMUSCULAR BLOCKADE**
An artist's conception depicting the acetylcholinesterase inhibitory action of Regonol at the neuromuscular junction.

*NDBA: Nondepolarizing Blocking Agent

**Brief Summary** (Please consult full package insert enclosed in every package, before using Regonol).

**INDICATIONS**—Regonol (pyridostigmine bromide) is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

**CONTRAINDICATIONS**—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

**WARNINGS**—Use with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

*Usage in Pregnancy*—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—Side effects are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As [illegible] any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—Prior or simultaneous administration of atropine sulfate (0.6 to 1.2 mg; I.V.) is recommended to minimize the side [illegible] essive secretions, bradycardia). Usually 10 or 20 mg of pyridos[illegible]mide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether.

**CAUTION**—Federal law prohibits dispensing without a prescription.

**HOW SUPPLIED**—Regonol is available in: 2 ml ampuls—5 mg/ml boxes of 10. NDC #0052-0460-10

Organon
A PART OF AKZONA INC.

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

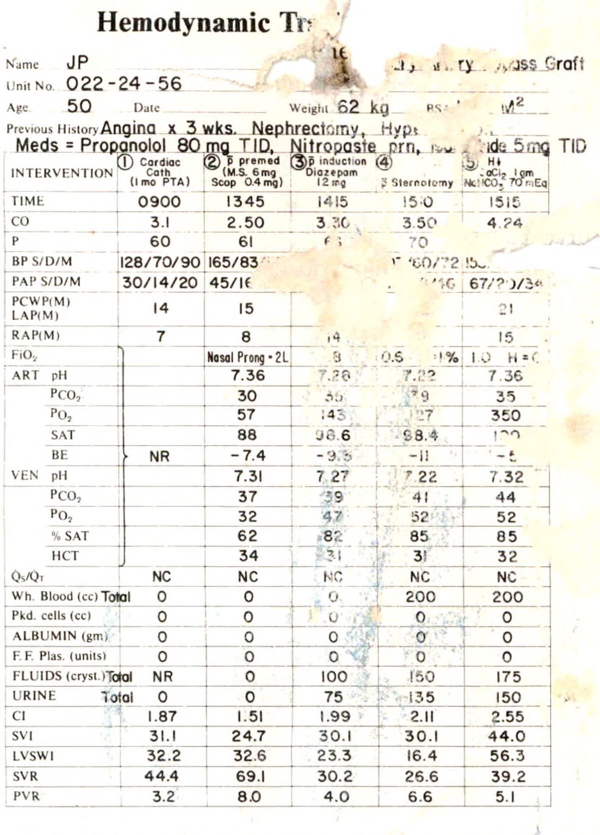
calculator. Cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) are rapidly computed (<30 seconds) by sequentially pressing calculator keys A to E. The time required to obtain one column of data (exclusive of blood gases) is dependent upon the number of cardiac output determinations performed. If cardiac output is determined in duplicate, [illegible] complete profile can be obtained in approximately 4 minutes.

Further insight regarding ventricular performance can then be obtained by plotting left ventricular stroke work index (LVSWI) and the [illegible] pulmonary capillary wedge pressure [illegible] function curve) (Figs 1 (right) and 2 (righ[illegible] patient, analysis of other derived [illegible] be important to diagnosis and man[illegible]

The following abbreviated [illegible] onstrate the use of the hemodynamic tracking system in two patients with mitral insufficiency. Although each patient developed an acute increase in PCWP, the clinical management was different based upon data ob[illegible] from the hemodynamic profiles.

## Case 1

A 66 [illegible] old woman with a diagnosis of coronary artery dise[illegible] 2+/4 intermittent mitral regurgitation (second[illegible] pillary muscle dysfunction) underwent coronary artery bypass surgery. The hemodynamic tracking profile (Fig 1) contains the original and derived data obtained during the cardiac catheterization and anesthesia. For simplicity, point 1 (cardiac catheterization) and point 2 (preinduction) are included only in the LVSWI plot. Following induction (point 3) and incision (point 4) the patient was relatively stable. Shortly after incision (enflurane 3%, $N_2O/O_2$, 2/2), "v" waves were noted in the pulmonary capillary wedge tracing (point 5). Review of the data obtained with



**Hemodynamic Tr[illegible]**

Name JP [illegible] Graft
Unit No. 022-24-56
Age 50 Date Weight 62 kg BS[illegible] M²
Previous History Angina x 3 wks. Nephrectomy, Hyp[illegible]
Meds = Propanolol 80 mg TID, Nitropaste prn, [illegible]ide 5mg TID

| INTERVENTION | ① Cardiac Cath (1 mo PTA) | ② p̄ premed (M.S. 6 mg Scop 0.4 mg) | ③ p̄ induction Diazepam 12 mg | ④ p̄ Sternotomy | ⑤ H↓ CaCl₂ 1gm NaHCO₃ 70 mEq |
|---|---|---|---|---|---|
| TIME | 0900 | 1345 | 1415 | 1500 | 1515 |
| CO | 3.1 | 2.50 | 3.30 | 3.50 | 4.24 |
| P | 60 | 61 | [illegible] | 70 | [illegible] |
| BP S/D/M | 128/70/90 | 165/83[illegible] | [illegible] | [illegible]60/72 | 15[illegible] |
| PAP S/D/M | 30/14/20 | 45/16[illegible] | [illegible] | [illegible]16 | 67/[illegible]/34 |
| PCWP(M) LAP(M) | 14 | 15 | [illegible] | [illegible] | 21 |
| RAP(M) | 7 | 8 | 14 | [illegible] | 15 |
| $FiO_2$ | NR | Nasal Prong - 2L | [illegible]8 | 0.5 [illegible]1% | 1.0 H = [illegible] |
| ART pH | | 7.36 | 7.28 | 7.22 | 7.36 |
| $PCO_2$ | | 30 | 35 | [illegible]9 | 35 |
| $PO_2$ | | 57 | 143 | 127 | 350 |
| SAT | | 88 | 98.6 | 98.4 | 1[illegible] |
| BE | | -7.4 | -9.[illegible] | -11 | -[illegible] |
| VEN pH | | 7.31 | 7.27 | 7.22 | 7.32 |
| $PCO_2$ | | 37 | 39 | 41 | 44 |
| $PO_2$ | | 32 | 47 | 52 | 52 |
| % SAT | | 62 | 82 | 85 | 85 |
| HCT | | 34 | 31 | 31 | 32 |
| $\dot{Q}_S/\dot{Q}_T$ | NC | NC | NC | NC | NC |
| Wh. Blood (cc) Total | 0 | 0 | 0 | 200 | 200 |
| Pkd. cells (cc) | 0 | 0 | 0 | 0 | 0 |
| ALBUMIN (gm) | 0 | 0 | 0 | 0 | 0 |
| F.F. Plas. (units) | 0 | 0 | 0 | 0 | 0 |
| FLUIDS (cryst.) Total | NR | 0 | 100 | 150 | 175 |
| URINE Total | 0 | 0 | 75 | 135 | 150 |
| CI | 1.87 | 1.51 | 1.99 | 2.11 | 2.55 |
| SVI | 31.1 | 24.7 | 30.1 | 30.1 | 44.0 |
| LVSWI | 32.2 | 32.6 | 23.3 | 16.4 | 56.3 |
| SVR | 44.4 | 69.1 | 30.2 | 26.6 | 39.2 |
| PVR | 3.2 | 8.0 | 4.0 | 6.6 | 5.1 |

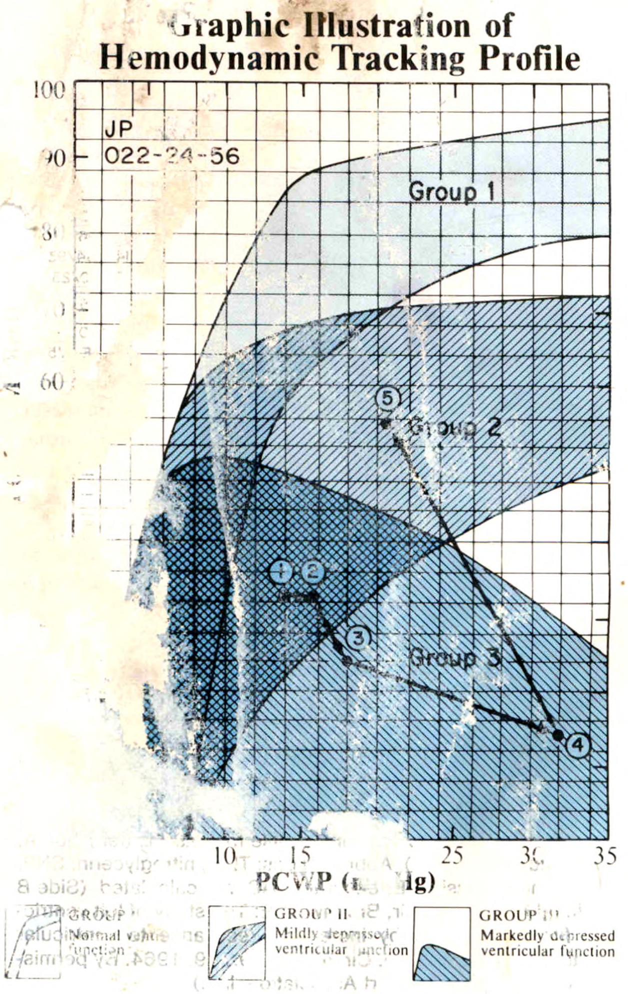


FIG 2. Hemodynamic Tracking Profile for Case 2: (left) side A; (right) side B (see text). Abbreviations are the same as in Fig 1; H, halothane; NR, not recorded. (Side B modified from Ross J Jr, Braunwald E: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 29:739, 1964. By permission of the American Heart Association, Inc.)

the hemodynamic tracking system, revealed a decreased cardiac output, an increased pulse rate, with a slightly increased mean arterial blood pressure and a markedly increased pulmonary capillary wedge pressure. Analysis of the derived indices revealed that cardiac index was maintained by a compensatory tachycardia, since the stroke volume index was decreased. The decreased stroke volume in conjunction with the elevated PCWP resulted in a significant decrease in left ventricular stroke work. The key to the successful management of this problem was the knowledge that the systemic vascular resistance was elevated in conjunction with altered cardiac function. Since the systemic vascular resistance was elevated (35.3 resistance units (RU)), an infusion of sodium nitroprusside was begun. The concentration of enflurane was decreased to 1% to reduce the myocardial depression associated with the anesthetic. The PCWP decreased to 11 mm Hg with a [illegible]ed improvement in ventricular performance (point 6). However, SVR was still elevated. Sodium nitroprusside infusion and enflurane concentration were further adjusted with a subsequent improvement in CO and SVR (point [illegible]). Shortly thereafter cardiopulmonary bypass was instituted. The remainder of the intraoperative course was uneventful.

## Case 2

A 50-year-old woman with a diagnosis of coronary artery disease and 1+/4 mitral regurgitation (secondary to mitral valve prolapse) underwent coronary artery bypass surgery The hemodynamic tracking profile (Fig 2) lists the pertinent physiologic data and derived variables. Following induction, anesthetic maintenance consisted of halothane, nitrous oxide/oxygen (2/3) and pancuronium. Due to blood loss, a slow transfusion (200 ml) was begun just prior to sternotomy. Immediately following sternotomy the PCWP rapidly increased to 32 mm Hg (point 4). In this case, the increased PCWP was accompanied by a slight increase of the cardiac output and pulse rate. Mean arterial blood pressure was maintained. Analysis of the derived variables revealed an increased PCWP accompanied by a decreased LVSWI. This is consistent with deteriorating left ventricular performance. Since SVR was only slightly elevated (26.6 RU), inotropic stimulation ($CaCl_2$ = 1 g) was employed, rather than vasodilator therapy. Acidemia (base excess = −11 meq/L) was treated with sodium bicarbonate, 70 meq. These interventions resulted in a dramatic improvement in ventricular performance (point 5). Cardiopulmonary bypass was instituted shortly thereafter and the remainder of the procedure was uneventful.

## Discussion

Sequential observations of changes in cardiovascular performance such as blood pressure, pulse rate, right atrial pressure, and pulmonary capillary wedge pressure are important. However, these do not render a complete "view" of the circulatory system. We believe that assessment of ventricular performance, in addition to CI, SVR, and PVR, and the response to therapy, is the foundation for sound physiologic management in the critically ill patient.

Although cardiac output itself is a useful circulatory measurement, the directional changes of the ventricular function curve are also an important estimate of the integration of cardiac performance.[1-5] In a clinical setting, sophisticated indices of ventricular performance are not yet routinely available. Ventricular function curves serve as a good means of quantitating function of the intact heart. This is due in part to the observation that the two axes of the ventricular function cu[illegible] qu[illegible]sively related to the major symptom con[illegible]ients with heart disease.[5] As the filling p[illegible] left ventricle (PCWP) rises, the sympto[illegible] pulmonary congestion appear. At low[illegible] ventricular stroke work, the signs [illegible]ppear. Stroke work is commonly [illegible]e of cardiac performance, since it represents [illegible]ernal work done by the ventricle. It [illegible] changes in ventricular function that are [illegible] when CI or SVI are used on the ordinate [illegible]tricular function curve. Thus, by using stroke work index, the ventricular function curve can provide a useful framework for relating [illegible] and physiologic observations. Usually a leftward and upward shift of the ventricular function curve has been regarded as an improvement in ventricular performance. In contrast, a shift down and to the right (group III) has been interpreted as a deterioration of ventricular performance.

Ross and Braunwald[6] constructed ventricular function curves relating left ventricular filling pressures and left ventricular stroke work index. From these data they described three classes of ventricular function: normal function (group I), mildly depressed ventricular function (group II), and grossly depressed ventricular function (group III). These curves were derived from data obtained under controlled conditions during cardiac catheterization. We have included these groups for "background" information so that the user may know the range of normal and abnormal ventricular function (Figs 1 (right) and 2 (right)).

In addition to changes in contractility, many interventions can also produce shifts of the ventricular function curve by alterations in preload, afterload, heart rate, and ventricular compliance.[3, 7] Therefore, stroke volume, stroke work, and other ejection phase measurements cannot be used as direct indices of contractility. Rather, these ejection phase indices can be useful in assessing directional changes in left ventricular function. This is especially important since in a given patient, one cannot be certain whether increasing cardiac contractility with inotropes (case 2) or reducing afterload with vasodilating agents (case 1) will be most efficacious. The hemodynamic tracking system helps evaluate a cardiovascular abnormality and rapidly analyze the response to therapy.

The programmable calculator offers high-level computational power inexpensively (TI-59 calculator cost = $210 to $300). It frees the anesthesiologist from the necessity of memorizing and recalling complex physiologic formulae during critical situations. In addition, operator error is reduced since only a few numbers have to be entered [illegible]er than fighting through a maze of formulae a[illegible] Although we chose five indices of cardiovascular performance which reflect acute changes and are amenable to clinical management, other [illegible]s can be easily inserted into the program to [illegible] the particular needs of the clinician.

Modifications in patient [illegible]st likely to succeed if they lead to more [illegible]nosis and a more stringent evaluation of ther[illegible] the operating room, data management should be simple, rapid, and inexpensive. The hemodynamic tracking system fits all three criteria.

### ACKNOWLEDGMENT

The authors wish to thank M. Cylkowski for contributing the body surface area segment of the program.

## Appendix 1

### Mathematical Computations Executed by the Hemodynamic Program

$$\text{BSA} = \text{Ht(cm)}^{0.725} \times \text{Wt (kg)}^{.425} \times 71.84 \times 10^{-4}$$

$$\text{CI} = \frac{\text{CO}}{\text{BSA}} = \text{L/min/m}^2$$

(normal = 3.0 ± 0.5 L/min/m²)

$$\text{SVI} = \frac{\text{CI}}{\text{P}} = \text{ml/beat/m}^2$$

(normal = 40 ± 7 ml)

$$\text{LVSWI} = (\overline{\text{BP}} - \overline{\text{PCWP}})(\text{SVI})(.0136) = \text{g-m/m}^2\text{/beat}$$

(normal = 35 − 85 g-m/beat/m²

$$\text{SVR} = \frac{\overline{\text{BP}} - \overline{\text{RAP}}}{\text{CI}} = \text{RU*}$$

(normal = 22 ± 4 RU)

$$\text{PVR} = \frac{\overline{\text{PAP}} - \overline{\text{PCWP}}}{\text{CI}} = \text{RU*}$$

(normal = 2 ± 1 RU)

where:

BSA = Body surface area
Ht = Height
Wt = Weight
CI = Cardiac index
CO = Cardiac output
P = Pulse rate
SVI = Stroke volume index
LVSWI = Left ventricular stroke work index
SVR = Systemic vascular resistance (index)
$\overline{\text{BP}}$ = Mean systemic blood pressure
PVR = Pulmonary vascular resistance (index)
$\overline{\text{RAP}}$ = Mean right atrial pressure
$\overline{\text{PAP}}$ = Mean pulmonary arterial pressure
$\overline{\text{PCWP}}$ = Mean pulmonary capillary wedge pressure

---

* To convert to dynes/sec·cm$^{-5}$ multiply by 79.9.

## Appendix 2

### User Instructions for Hemodynamic Profile

| Step | Procedure | Enter | Press | Display |
|---|---|---|---|---|
| 1 | Enter program | | | 1. |
| 2 | Enter weight in kg | WT | 2nd A | 0 |
| | or in pounds | | 2nd A, R/S | |
| | height in cm | HT | 2nd B | BSA |
| | or in inches | | 2nd B, R/S | BSA* |
| 3 | Enter body surface | BSA | STO 01 | BSA (m²)† |
| 4 | Enter cardiac output | CO | STO 02 | CO (L/min) |
| 5 | Enter pulse rate | P | STO 03 | P (beats/min) |
| 6 | Enter mean blood pressure | $\overline{\text{BP}}$ | STO 04 | $\overline{\text{BP}}$ (mm Hg) |
| 7 | Enter mean $\overline{\text{PAP}}$ | $\overline{\text{PAP}}$ | STO 05 | $\overline{\text{PAP}}$ (mm Hg) |
| 8 | Enter mean $\overline{\text{PCWP}}$ | $\overline{\text{PCWP}}$ | STO 06 | $\overline{\text{PCWP}}$ (mm Hg) |
| 9 | Enter mean right arterial pressure | $\overline{\text{RAP}}$ | STO 07 | $\overline{\text{RAP}}$ (mm Hg) |
| 10 | Compute CI | | A | CI (L/min/m²) |
| 11 | Compute SVI | | B | SVI (ml/m²/beat) |
| 12 | Compute LVSWI | | C | LVSWI (g-m/m²/beat) |
| 13 | Compute SVR | | | SVR (RU)‡ |
| 14 | Compute PVR | | | PVR (RU)‡ |

---

* To obtain BSA for inches, the [illegible] inches is entered and 2nd B is pressed. The display will the[illegible]intermediate result (not BSA). BSA is obtained by [illegible] S. BSA will be displayed and automatically stored ([illegible]

† If already known BSA can be e[illegible]nto the storage register (STO 01) ([illegible]ep 3).

‡ Indexed resistance units are used to o[illegible] that is comparable in patients of varying size (see App[illegible] for normal values).

ANESTH ANALG
59:175–177, 1980

# Effects of Low Concentrations of Nitrous Oxide on Rat Fetuses

**Erica Vieira,* P. Cleaton-Jones,† J. C. Austin,‡ D. G. Moyes,§ and R. Shaw||**

---

VIEIRA, E., CLEATON-JONES, P., AUSTIN, J. C., MOYES, D. G., AND SHAW, R.: Effects of low concentrations of nitrous oxide on rat fetuses. Anesth Analg 59:175–177, 1980.

The long-term inhalation of air polluted with nitrous oxide has been implicated in spontaneous abortions and fetal abnormalities in operating room personnel. Studies with 1% and 0.5% $N_2O$ in air have confirmed the adverse effects of dilute concentrations of $N_2O$ in pregnant rats. The present study was designed to determine the threshold concentration of nitrous oxide necessary to produce adverse responses in pregnant rats. Wistar albino rats were mated in an environmental chamber and conception confirmed by vaginal smears. Immediately thereafter, the rats were randomly divided into control and experimental groups. The control rats were exposed for 19 days to oil-free compressed air in an environmental chamber at a flow rate of 8.5 air changes per hour. Experimental animals were exposed continuously under identical conditions to concentrations of 0.0, 0.1%, 0.5%, or 0.025% $N_2O$. On day 19 the gravid rats were killed. The corpora lutea of pregnancy were counted and related to the number of fetuses in the uterus. Fetuses were fixed, cleared, and their skeletons stained with alizarin red. Litter size, frequency of fetal resorption, and fetal crown rump measurements were significantly different following exposure to 0.1% $N_2O$ than they were in control rats or in rats exposed to 0.05% or 0.025% nitrous oxide, neither of which had any fetal effects. The suggested threshold level of 30 ppm (0.03%) $N_2O$ in humans may be unrealistically low.

**Key Words:** ANESTHETICS, Gases: nitrous oxide; TOXICITY, Trace concentrations; PREGNANCY: abortion and teratogenicity.

---

THE LONG-TERM inhalation of air polluted with anesthetic gases has been suggested as a cause of spontaneous abortions and fetal abnormalities in humans.[1, 2] One of the anesthetic gases thought to play a significant role is nitrous oxide; it has been shown to have teratogenic effects in chick embryos[3] and to have an adverse effect on pregnant rats.[4–6] The present study was undertaken to study the effects of the continuous exposure throughout pregnancy of rats exposed to 0.1% (1000 ppm), 0.05% (500 ppm), or 0.025% (250 ppm) nitrous oxide/air mixtures (v/v) in an attempt to define the threshold level of nitrous oxide necessary to produce adverse effects in pregnant rats.

## Methods and Materials

There were 48 Wistar strain female albino rats weighing 150 g each used in the study. They were assigned at random to a control group and to three experimental groups of 12 rats each. All were housed in plastic cages with mesh floors in two environmental chambers supplied with oil-free air from a diaphragm compressor. The control group was exposed to air only and the experimental groups to 0.1%, 0.05% or 0.025% nitrous oxide in air (v/v), respectively. The study was performed in two stages, since there were two environmental chambers, and before each stage the rats were acclimatized for 7 days in the chambers, during which periods only air was supplied.

Wistar albino female nulliparous rats were mated in the environmental chambers by placing them over-

---

* Dip Microbiol, Technician.

† BDS, MBBCh, DA, PhD, Professor and Director.

‡ BVSc, Chief Research Officer, MRC/Dental Research Institute, University of the Witwatersrand, Johannesburg.

§ FRCS, MBChB, FFARCS, Professor and Head of Department.

|| BSc, Technican, Department of Anaesthesia, Baragwanath Hospital, Johannesburg.

Received from the Dental Research Institute, School of Dentistry, 1 Jan Smuts Avenue, Johannesburg 2001, South Africa. Accepted for Publication November 1, 1979.

Reprint requests to Ms Vieira.

night together with a male rat, in the breeding ratio of one male to four females per cage. Each morning vaginal smears from each female were examined microscopically for the presence of spermatoza. This indicated that mating had occurred the previous evening. Since mating in the rat only occurs during a short 12-hour estrus period, evidence of mating may be used to assume that conception had taken place. The gestation period of the Wistar albino rat is 19 to 21 days.

Groups of 12 mated rats were placed in the environmental chambers and the nitrous oxide was added to the air supply by means of a calibrated flow meter to the required concentration. Three times during the experimental period nitrous oxide concentrations were monitored by gas sampling from the rat cages and their levels were determined with a katharometer in a Pye Unicam gas chromatograph. The $N_2O$ levels closely approximated the required concentrations and were equal at each cage level. Temperature and humidity were controlled by setting the inflow rate of gases at a level adequate to produce 24 changes per hour. This maintained the environment in the chambers within reasonable limits for the comfort and health of the animals. A commercial cubed rat diet (Epol rat cubes) and water were available ad libitum to all the animals during the acclimatization and experimental periods.

The mated rats were continuously exposed to the gases except for a brief 10-minute period each day when the environmental chambers were opened to remove feces and urine and to replenish food and water. The positions of the cages in racks within the chambers were rotated daily to ensure that any chamber effects that might have been related to cage position were evenly imposed on all the rats. No difference in the food and water consumption between control and experimental rats was noted during the experimental period.

The rats were killed on day 19 of their pregnancies by carbon dioxide administration. The abdominal viscera were exposed and detailed examination of ovaries and gravid uteri were carried out using a dissecting microscope. The number of corpora lutea of pregnancy was counted by surface examination and compared with the number of fetuses present. When these did not correspond the uterus was examined for involuting placentation sites, which indicated that fetal resorption had occurred during pregnancy. The fetuses from each rat were sexed by external characteristics, and each fetus was examined externally and internally using a dissecting microscope. They were then fixed in 10% formol saline, cleared in 0.5% potassium hydroxide, and stained with alizarin red for a systematic examination of the fetal skeletons. Anatomical variations were noted. When variations were found the fetuses were compared with their littermates and with litters belonging to the control group. Crown-rump measurements were made of each fetus.

## Statistical Analysis

The experimental format was planned as a two-way nested design. The statistical analysis of fetal weights and crown-rump measurements thus comprised an analysis of variance based on this design. For litter size, fetal resorption, and skeletal malformations the Student's *t*-test, Chi square test, and Fisher's exact probability test were used, respectively.

## Results

A total of 424 fetuses were produced by the four groups of rats; 120 in the control group; 66 in the group exposed to 0.1% nitrous oxide; 118 in the group exposed to 0.05%; and 120 in the group exposed to 0.025% nitrous oxide (Table).

The litter size in the group of gravid females breathing 0.1% nitrous oxide was almost half that compared to the control group and the other two experimental groups. This difference was statistically significant at the 0.01% level.

Fetal resorption occurred in the group exposed to 0.1% nitrous oxide where four of the 12 dams each showed resorption of one fetus. This was statistically significant at the 0.01% level. No fetal deaths or resorptions were found in the control group or the dams exposed to 0.05% or 0.025% nitrous oxide.

Crown-rump measurements of fetuses from dams exposed to 0.1% nitrous oxide were significantly less than comparable measurements in fetuses of the control group and in the groups exposed to 0.05% or 0.025% nitrous oxide ($p < 0.05$). In contrast, however, no significant difference was found between body weights of fetuses of the control and of any of the experimental groups exposed to nitrous oxide. No abnormalities of internal organs and no skeletal anomalies were observed in any of the fetuses in the control group or in the groups exposed to 0.05% or 0.025% nitrous oxide in air. Skeletal abnormalities were found only in the group exposed to 0.1% ($p < 0.05$). These abnormalities were in the form of rib malformations and abnormal vertebrae columns. There was no significant difference in the male:female ratios.

**TABLE**

**Litter Size, Crown-Rump Measurements, and Fetal Resorptions of Control and Experimental Groups of Rats**

| | Litter size* | | | Crown-rump measurements (mm) | | | Resorptions | |
|---|---|---|---|---|---|---|---|---|
| | n | Range | Means ± SD | n† | Range | Means ± SD | n† | No. of resorptions |
| Compressed air | | | | | | | | |
| Control | 12 | 9–13 | 11.3 ± 1.4 | 120 | 32–50 | 44 ± 1.4 | 120 | None |
| Nitrous oxide | | | | | | | | |
| 0.1% | 12 | 3–9 | 6.3 ± 4.0 ($p < 0.001$‡) | 66 | 30–45 | 35 ± 1.6 ($p < 0.05$‡) | 66 | 4 ($p < 0.001$‡) |
| 0.05% | 12 | 9–13 | 11.0 ± 1.4 (NS§) | 118 | 32–50 | 43 ± 1.3 (NS) | 118 | None (NS) |
| 0.025% | 12 | 8–13 | 11.3 ± 1.3 (NS) | 120 | 32–50 | 43 ± 1.4 (NS) | 120 | None (NS) |

* Numbers of fetuses in n = the number of pregnant rats studied.

† Number of fetuses studied.

‡ Significant difference between results observed in rats exposed to 0.1% $N_2O$ and results observed in control rats and rats exposed to 0.05% and 0.025% $N_2O$.

§ NS, no significant differences observed in control rats and in rats exposed to 0.05% and 0.025% $N_2O$.

## Discussion

The reduction in fetal number per litter in the group of rats exposed to 0.1% nitrous oxide was accompanied by fetal resorption, an observation which was confirmed by the fact that the number of corpora lutea of pregnancy recorded in the ovaries of the rats corresponded exactly to the number of implantation sites found in the uterine horns. This finding suggests that the critical nitrous oxide concentration that will cause fetal death and resorption in rats, when breathed continuously during pregnancy, lies between 0.05% and 0.1%. Fink et al[3] have reported that in rats and man there is a similarity in the susceptibility of the nervous and hemopoietic systems to depression by nitrous oxide, and they have suggested that studies of the effects of nitrous oxide in the rat may indicate possible effects of nitrous oxide in man. The results of our study, viewed in this light, suggest that the arbitrary threshold limit value of 30 ppm (v/v), ie, 0.003% nitrous oxide, suggested by Whitcher et al[7] may be well below the actual safety limits. Levels of nitrous oxide pollution higher than this may be innocuous to man, especially if personnel are only exposed intermittently, although this may depend on susceptibility of a fetus at various stages of pregnancy.

### REFERENCES

1. Cohen EN, Weldon Bullville J, Brown BW: Anesthesia, pregnancy and miscarriage. Anesthesiology 35:343-347, 1971
2. Vessy MP: Epidemiological studies of the occupational hazards of anesthetics—a review. Anaesthesia 33:430-435, 1978
3. Fink BR, Sheppard TH, Landau RJ: Teratogenic activity of nitrous oxide. Nature 214:146-148, 1967
4. Corbett TH, Cornell RG, Endres JL, et al: Effects of low concentrations of nitrous oxide on rat pregnancy. Anesthesiology 39:299-302, 1973
5. Vieira E, Cleaton-Jones PE, Austin J, et al: Intermittent exposure of gravid rats to 1% nitrous oxide and the effect on the postnatal growth of their offspring. S Afr Med J 53:106-108, 1978
6. Vieira E: Effect of 0.5% nitrous oxide on gravid rats. Br J Anaesth 51:283-287, 1979
7. Whitcher CE, Cohen EN, Trudell JR: Chronic exposure to anesthetic gases in the operating room. Anesthesiology 35:348-351, 1971

ANESTH ANALG
59:178–185, 1980

# Contribution of Asynergic Contraction to Halothane-Induced Myocardial Depression

**N. Ty Smith, MD,* Neil B. Ingels, Jr., PhD,† George T. Daughters II, MS,‡ and Lewis Wexler, MD§**

SMITH, N. T., INGELS, N. B., JR., DAUGHTERS, G. T., II, AND WEXLER, L.: Contribution of asynergic contraction to halothane-induced myocardial depression. Anesth Analg 59:178–185, 1980.

We investigated the possibility that myocardial asynergy (dyscoordinate contraction) is a contributing mechanism to the impairment of cardiac function produced by halothane. Coronary cineangiograms were performed in seven dogs, awake and at 1, 2, and 3 MAC halothane. The relative motions between four arterial bifurcations (six segments) were plotted as an indication of changing ventricular dimensions. To quantitate ventricular asynergy, we calculated anisotropy (AI) and asynchrony (AS), the coefficient of variation of mean shortening ($\bar{S}$) and of mean time to half shortening ($\bar{T}_{50}$), respectively, of the six segments. From these a myocardial performance index (MPI) was derived: MPI = $\bar{S}$/AI + $\bar{T}_{50}$ + AS.

In general, $\bar{S}$ and MPI decreased with increasing halothane concentration. Anisotropy showed a trend, although usually insignificant, toward increasing, while AS did not change.

These observations have two implications. First, asynergy of contraction contributes little, if anything, to halothane-induced impairment of myocardial performance. Second, changes in measurements of intact cardiac performance, such as $dP/dt_{max}$, may be reasonably valid during halothane, provided loading conditions are taken into account.

**Key Words:** ANESTHETICS, Volatile: halothane; HEART: myocardial function.

WITH more than 200 papers attesting to the fact, it is well known that halothane depresses cardiac function. Several, often interrelated, mechanisms could be responsible for this phenomenon in the intact animal: a direct myocardial depression via the contractile element; a decrease in energy synthesis or utilization; an effect upon the cardiac cellular membrane; a shift in myocardial $Ca^{2+}$ concentrations; partial excitation-contraction uncoupling; central nervous system-mediated depression; decreased preload; and/or increased asynergy of contraction. Each of these possibilities has been investigated except the last.[1-17] We report such a study in dogs and conclude that asynergy of contraction has little, if any, influence on cardiac function during halothane anesthesia.

## Methods and Materials

### Protocol

Seven mongrel dogs, weighing 14 to 23 kg each, were selected on the basis of their ability to emerge

---

* Professor of Anesthesia, University of California, San Diego, Veterans Administration Hospital, San Diego.

† Senior Research Associate, Palo Alto Medical Research Foundation, Palo Alto.

‡ Research Associate, Palo Alto Medical Research Foundation, Palo Alto.

§ Associate Professor of Radiology, Stanford University Medical Center, Stanford.

Supported in part by the Medical Research Service of the Veterans Administration.

Received from the Department of Anesthesia, University of California, San Diego; Veterans Administration Hospital, San Diego; Palo Alto Medical Research Foundation, Palo Alto; and Department of Radiology, Stanford University. Accepted for publication November 13, 1979.

Reprint requests to Dr. Smith, Anesthesia Department 112B, Veterans Administration Hospital, 3350 La Jolla Village Drive, San Diego, CA 92161.

quietly from halothane anesthesia. These animals were then trained to lie still for at least 30 minutes following anesthesia.

For the definitive experiment, each animal was anesthetized with 1% end-tidal halothane in $O_2$, as determined by a Beckman LB-I infrared gas analyzer. An endotracheal tube was inserted without the aid of a neuromuscular blocking agent. Ventilation was controlled with a Harvard ventilator to maintain arterial pH between 7.37 to 7.43 and arterial $P_{CO_2}$ between 31 to 34 torr, as measured by an Instrumentation Laboratories 113-52 blood gas analyzer.

The left coronary ostium was cannulated via the left femoral artery using a preformed polyethylene catheter (o.d. 2.4 mm). This catheter was left in place for the duration of the study. A unipolar electrode (Elecath) driven by a Medtronics 5800 pacemaker was inserted into the right atrium via the right femoral vein with ECG ground as the indifferent electrode. A trial pacing was performed in each animal during anesthesia at a rate equal to the "conscious control" rate.

Single plane coronary cineangiograms were obtained in the left lateral projection using the 5" mode of a Phillips dual mode image intensifier, and a 35-mm Arriflex camera at 76 frames/sec on Kodak XX film. Single injections of 5 ml of meglumine diatrizoate (Renografin-76) were used for coronary visualization. The cinefluorographic sequence was begun several beats before injection and continued until the contrast medium was cleared from the coronary circulation. Ventilation was held in the anesthetized animals at end expiration during contrast injections.

After insertion of the catheters, the skin incision sites were infiltrated with 1% lidocaine. The anesthetic was discontinued and the animal hyperventilated so that it might tolerate the endotracheal tube for a longer period of time. When the animal finally expelled the tube, the end-tidal halothane concentration was usually less than 0.25%. After the animal rested and breathed spontaneously for at least an additional 10 minutes, and when heart rate and arterial pressure were steady for at least 5 minutes, measurements were taken, including a coronary angiogram. The animal was then reanesthetized and measurements repeated at 1, 2, and 3 MAC (1 MAC = 0.9%) end-tidal halothane in the dog.[18] End-tidal concentrations were maintained for 15 minutes for each step.

## Analysis

To determine relative motion between fixed points on the myocardium, bifurcations of the coronary arteries were selected along the anterior and posterior interventricular and marginal arteries (Fig 1). These branching points have been shown by Kong and associates[3] to be relatively fixed in relation to the epicardial surface when compared with markers sutured on the epicardium near the branching points. Hence, they act as radiopaque markers, but in a closed-chest preparation. With four points, six combinations of points or myocardial segments are possible. The relative motion between branching points during the cardiac cycle is a reflection of myocardial shortening along that axis. For example, branching points along the left anterior interventricular artery indicate longitudinal shortening, whereas motion between the posterior interventricular and anterior interventricular arteries would indicate circumferential or transverse shortening.

Frame-by-frame analysis of the cine-films was performed on a Vanguard projecting film digitizer. Linear magnification was 20 times, and the film plane resolution of the digitizer is 5 μm. Two independent readings were obtained for each point in each cineframe. More than 12,000 frames were analyzed in this way. Distances between the Ith and Jth points were calculated for each reading of each frame by a Fortran program on an IBM 360-50 computer according to the formula:

$$D(I,J) = \sqrt{(X(I) - X(J))^2 + (Y(I) - Y(J))^2}$$

The computer yielded a TV display for each axis of shortening. An example is given in Fig 2. The first three beats after appearance of the dye were measured. The instantaneous lengths of each I,J vector

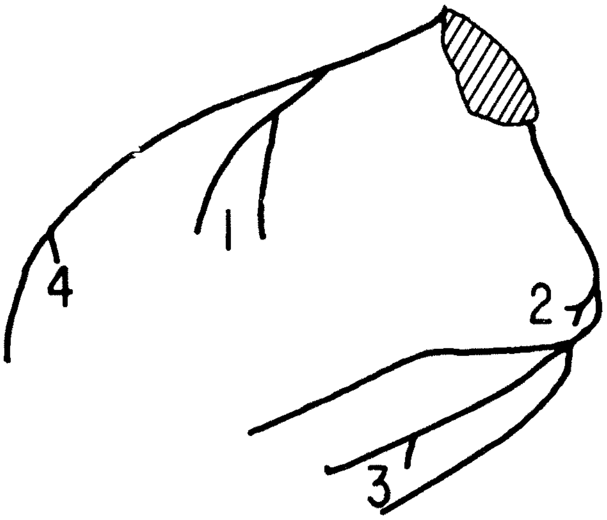


FIG 1. Coronary arterial bifurcations used as markers for the cineangiographic determination of dimensional changes.

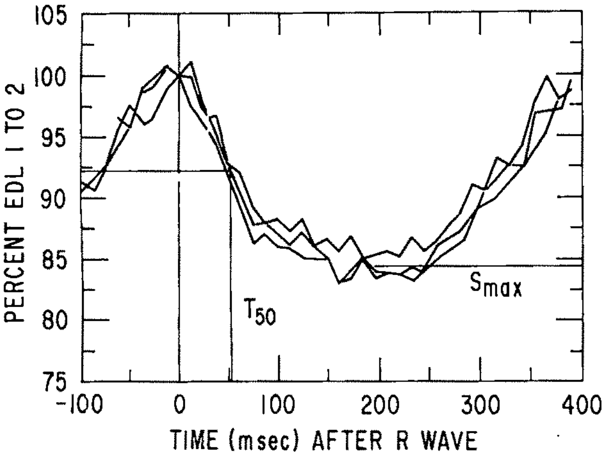


FIG 2. Dimensional changes between bifurcations 1 and 2 (see Fig 1) for three consecutive beats after the injection of contrast medium. Halothane concentration is 1 MAC. Vertical line represents R wave. EDL, End-diastolic length; $T_{50}$, time to half of maximal shortening; $S_{max}$, maximal shortening.

were normalized to end-diastolic length (EDL) for each beat and displayed as a percentage of EDL as a function of time. End-diastolic length was defined for each vector as the maximal segmental length attained during the Q-R interval of the electrocardiogram. Note the reproducibility in the curves in the three consecutive beats shown. This was true for all runs and during repeated measurements under the same conditions. In the awake animals, respiration could not be controlled and slight variations occurred which may have been the result of diaphragmatic motion and baroreceptor influences.

Asynergy was described in terms of anisotropy (AI) and asynchrony (AS), which were, in turn, used to derive a myocardial performance index (MPI). To determine AI, we measured the maximum shortening of each of the six segments (Fig 2). Then we divided the mean shortening ($\bar{S}$) of these six segments by the standard deviation to obtain the coefficient of variation = AI. As used here, anisotropy refers to the difference in maximum strain at varying angles on the surface of the heart. Of course, all hearts are anisotropic to a degree, since they are not uniformly contracting spheroids. We defined AS as the mean of the time to half-shortening ($\bar{T}_{50}$) (see Fig 2) divided by the standard deviation. Thus, if all the segments shorten by half in the same length of time, we say we are dealing with a perfectly synchronous heart, and the value of asynchrony is zero. The MPI was calculated as:

$$\text{MPI} = \frac{\bar{S}}{\text{AI} + \bar{T}_{50} + \text{AS}}$$

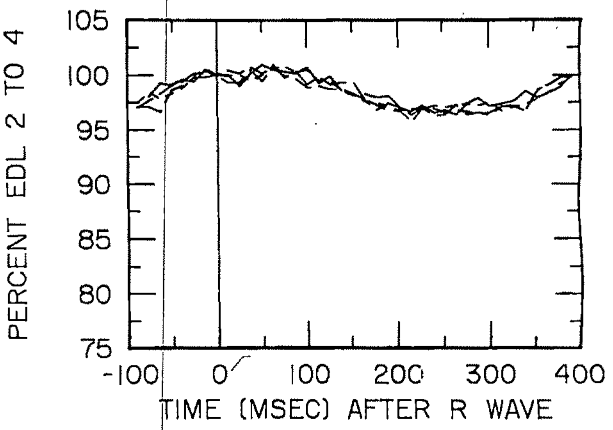


FIG 3. Dimensional changes between bifurcations 2 and 4 (see Fig 1) at 3 MAC. Vertical line represents R wave. EDL, End-diastolic length.

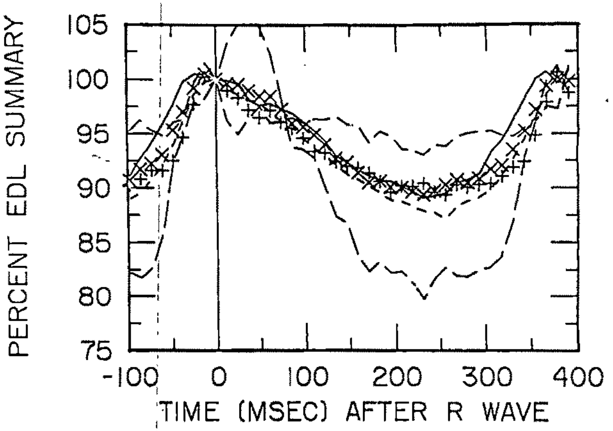


FIG 4. Mean of six segmental shortenings (segments 1-2, 1-3, etc) from one animal at 1 MAC halothane. Note the variability in extent, rate, and timing of contraction. Vertical line represents R wave. EDL, End-diastolic length.

To compare the awake values with those obtained from the different levels of anesthesia, we calculated the mean and the standard deviation of all animals for $\bar{S}$, AI, $\bar{T}_{50}$, AS, and the MPI. Differences were evaluated by the paired *t*-test, with $p < 0.05$ being selected as significant.

## Results

Fig 2 shows the dimensional changes during 1 MAC halothane, and Fig 3 the changes during 3 MAC halothane. The decrease from Fig 2 to Fig 3, in extent and velocity of shortening, is obvious. In the latter figure, it appears as if the heart were doing little except expanding and shrinking in a sinusoidal fashion. In Figs 4 and 5, there is obvious asynchrony (AS) and anisotropy (AI) as defined above. In fact, one segment actually expands during systole. Are the two contractions different from each other in the extent of asynergy? Figs 6 to 10 show the changes in $\bar{S}$, $T_{50}$ AI, AS, and MPI resulting from anesthesia and from increasing concentrations. Maximum shortening decreases with halothane and with increasing concentration (Fig 6), the differences between each step being significant, except for that between 2 and 3 MAC. Time of shortening ($\bar{T}_{50}$), on the other hand, did not change significantly (Fig 7). The coefficient of variation of shortening (anisotropy) showed a trend toward increasing with increasing concentration (Fig 8). However, the only significant difference was between awake and 3 MAC halothane. The coefficient of variation of time (asynchrony) did not change significantly under any of the conditions (Fig 9).

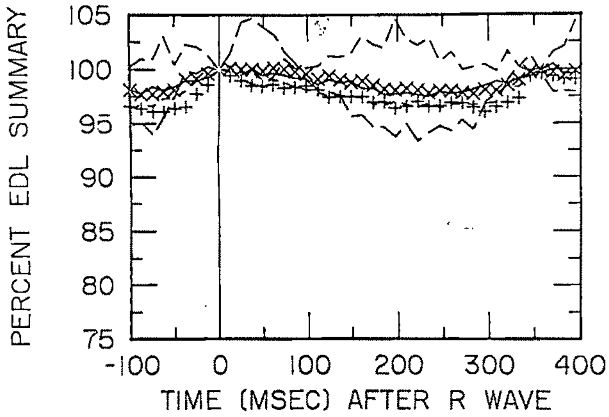


FIG 5. Mean of six segmental shortenings (segments 1-2, 1-3, etc) from one animal at 3 MAC halothane. Asynergy still persists.

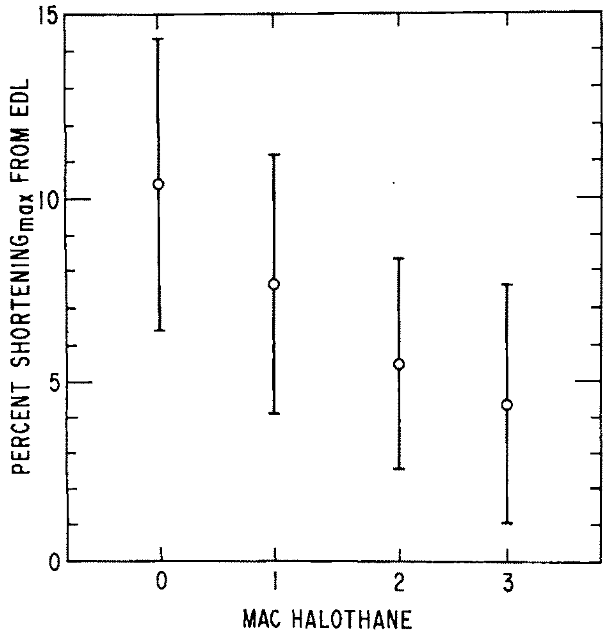


FIG 6. Mean maximum shortening from end-diastolic length as a function of halothane concentration in seven animals. Bars represent standard deviations.

The MPI showed a tendency to decrease with anesthesia and with increasing concentration (Fig 10). However, the difference was not significant between 1 and 2 MAC nor between 2 and 3 MAC halothane.

## Discussion

### Methodologic Errors

There are several possible sources of error that must be understood and, if possible, compensated for in this technique. For example, two criteria should be applied in selecting the segments to be used in this analysis.[20] First, the same ventricular sites should be used in each individual if values of asynergy are to be compared among individuals. Second, only the segments whose length is greater than 100 times the measurement error should be used, to minimize the effect of this error.

Another source of error is reflected in the deviation from smoothness in the curves shown in Figs 2 to 5. This deviation is due to uncertainties in localizing bifurcations during the digitizing step. It can be shown that the standard deviation in normalized length (% EDL) due to measurement error is given by

$$\sigma_m = \frac{\sigma_e}{\text{EDL}\sqrt{2/N}}$$

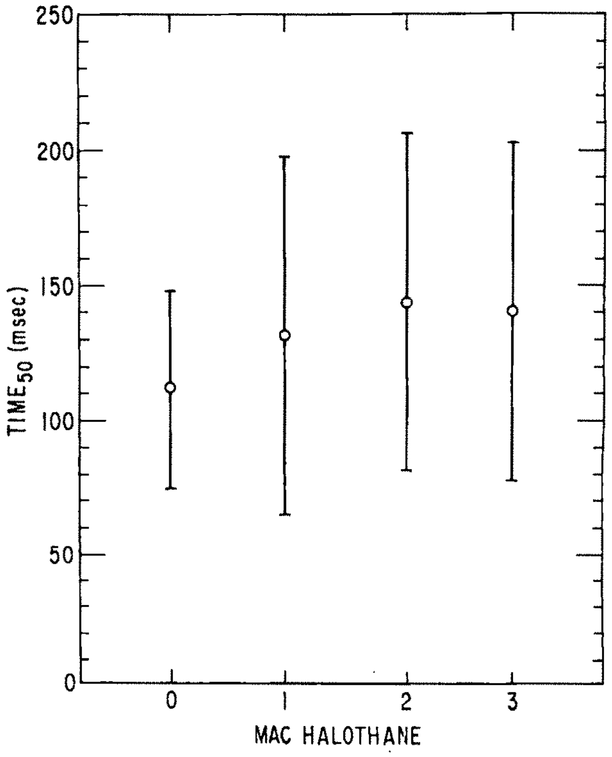


FIG 7. Time to 50% maximum shortening from end-diastolic length as a function of halothane concentration in seven animals. Bars represent standard deviations.

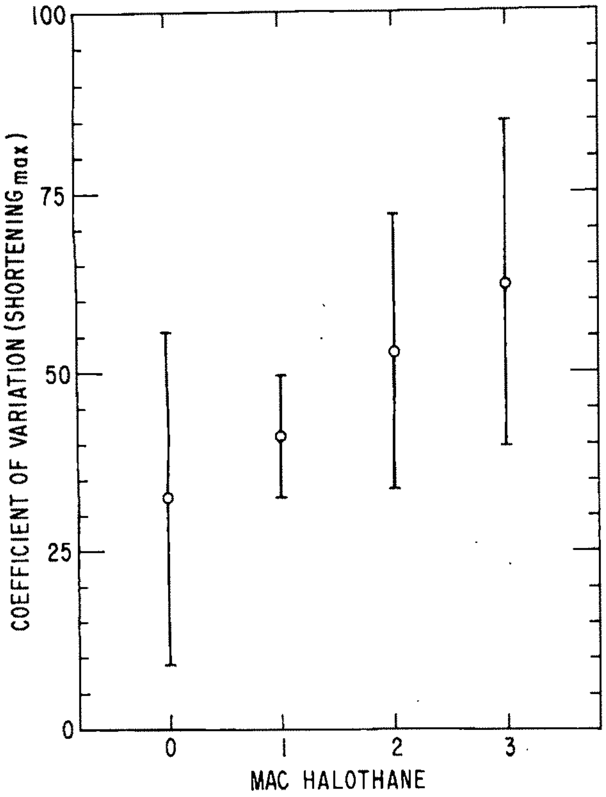


FIG 8. Coefficient of variation of shortening (anisotropy) as a function of halothane concentration in seven animals. Bars represent standard deviations.

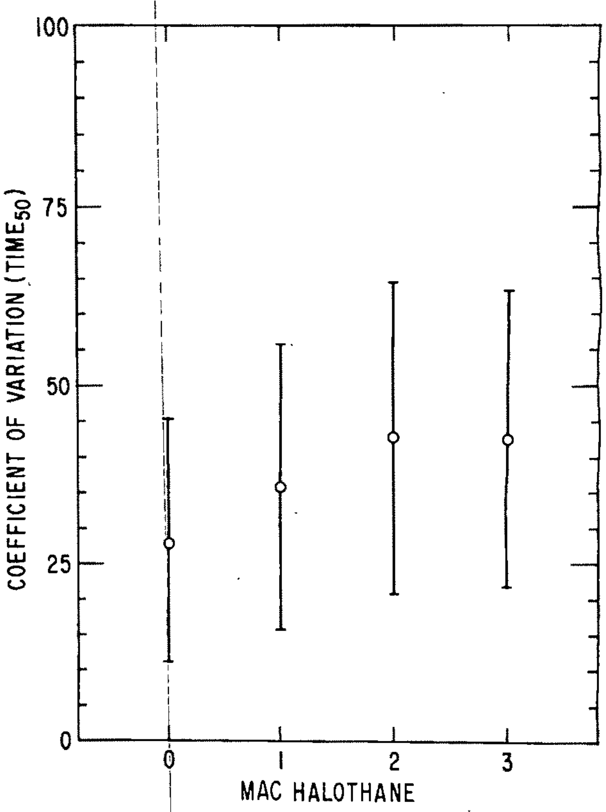


FIG 9. Coefficient of variation of time to 50% shortening (asynchrony) as a function of halothane concentration in seven animals. Bars represent standard deviations.

The value $\sigma_m$ can be made arbitrarily small by making N arbitrarily large (repeated measurements), or by filtering the time series, or both.

The image formed in any x-ray system is a distorted projection of the actual object; since the beam is not parallel, the imaging system is imperfectly aligned with the principal axis of the system, and the image intensifier adds geometric distortion, especially in the "magnifier" mode, where the magnification factor varies up to 30% over the field. A map of these distortions is often necessary, so that corrections may be made in the data-processing step.[21] Such corrections are unnecessary in this study, since points of interest are confined to a limited region in space during the cardiac cycle. Thus, the distortion remains relatively constant for a given segment, and tends to cancel out when the length is normalized to end-diastolic length.

The most serious error in the measurement of myocardial shortening with the single-plane technique is due to rotation of the segments under study relative to the projection plane during the cardiac cycle. Rotation error is minimized by judicious choice of the projection angle, that is, subject position, such that the bifurcations to be studied lie, as closely as possible, in a plane parallel to the projection plane. It has been determined[22] that the projection angle of choice can be found by overlaying, as closely as possible, the vessel under study in the right anterior oblique (RAO) projection during a test injection, then rotating the subject 90° from this angle into the left anterior oblique (LAO) projection. Using this approach, an average $\theta$ in six segments was determined as 12.5° (SD 9.3°).

These values, along with the mean $\sigma$ of 0.46° (SD 4.3°) demonstrated in the biplane studies of Harrison et al,[23] were used in a Monte Carlo statistical analysis. The correction factor exhibited a mean value of 1.0051 with SD 0.0235. Thus, the mean error due to rotation if 0.51% EDL with SD 2.35% EDL.

Since the errors from distortion and rotation are statistically independent and the measurement error can be made arbitrarily small by smoothing, the combined mean error becomes 0.54% EDL ($\epsilon_d + \epsilon_r$) with SE 2.41% EDL.

Thus, in order to assert that % EDL values from any

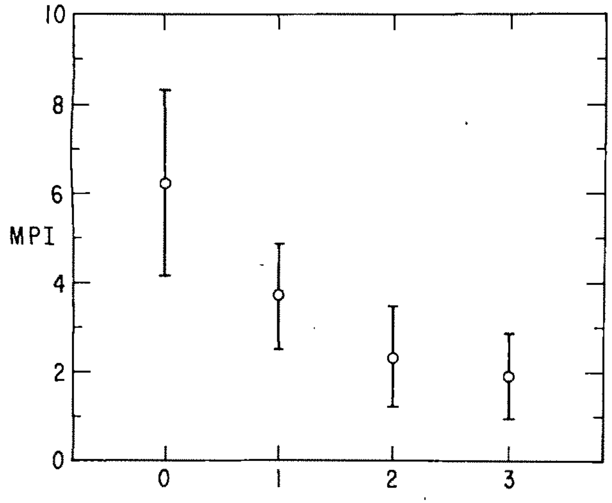


FIG 10. Myocardial performance index (MPI—see text) as a function of halothane concentration in seven animals. Bars represent standard deviations.

two myocardial segments are significantly different at the 80% and 95% confidence levels, respectively, it is necessary that these values differ by a minimum of 4.4% and 6.7%. This defines the $p < 0.2$ and $p < 0.05$ diagnostic limitations of this single-plane approach in detecting abnormal segmental shortening.

Since the coronary arteries are located primarily on the epicardial surface, it is important to determine whether their motions accurately follow the motions of the underlying myocardium. "Loose" coupling of the arteries to the myocardium could result in sizeable errors, due to myocardial shear during the cardiac cycle. Kong et al[19] observed that motions of bifurcations and surgically affixed epicardial clips correlated well (R = 0.85) with a standard error of estimate of 2.2%. Their study, however, did not measure the shear between the epicardium and underlying myocardium. Feigl and Fry[24] did show that shearing through the thickness of ventricular wall is minimal except during the brief isovolumic phase of contraction and relaxation.

Daughters et al[22] demonstrated that any relative motion of the myocardium and epicardium does not contribute significantly to error in our type of study, since the motions of bifurcations and myocardial markers also are well correlated (R = +0.85, a standard error of estimate of 2.34%). Comparing the regression equation of Kong with that of Daughters, the disagreement of proportionality constant (0.90 vs 0.74) is consistent with the concept of systolic wall thickening during the cardiac cycle.

A total of six vectors (1-2, 1-3, 1-4, 2-3, 2-4, 3-4), each representing a myocardial segment between the previously defined coronary branching points, were available for analysis. The four principally circumferential vectors (1-2, 1-3, 2-4, 3-4) were selected for the synergy analysis for two reasons. First, Streeter et al[25] have shown that the proportion of circumferential to longitudinal fibers is 10:1 in the canine heart. Second, Ingels, et al[26] have observed in studies of anesthetized, thoracotomized dogs that the principal mode of contraction of the canine ventricle is a vigorous motion of the lateral free wall toward a relatively fixed septum. These four vectors are most sensitive to such dynamics.

From the above considerations, it is concluded that myocardial segmental shortening can be determined from single-plane coronary cineangiograms with suitable accuracy. An important criticism of this method of quantifying ventricular synergy, however, is that the location and limited number of points chosen could overlook important regions of dysfunction, particularly in the posterior aspect of the left ventricle. The points chosen in this study emphasize anterior wall dynamics since it has been suggested[21] that anterior wall contraction makes a more important contribution to left ventricular ejection than other regions. Additional studies at different projection angles utilizing more bifurcations (or the use of biplane cineradiograms) could eliminate this criticism in cases where more extensive characterization of the ventricle was deemed necessary.

Does the injection of contrast material affect the very variable we are trying to measure? When implanted tantalum myocardial markers are used[22] so that preejection beats can be compared with postejection beats it can be shown that, with the dye we used, there is no significant effect of the contrast agent on myocardial dynamics during the period when the distances between the bifurcations are measureable.[22] This is in agreement with Kong et al[19] who also showed no effect for five to six beats after injection.

Two comments should be made about the experimental protocol itself. First, we realize that our "conscious control" does not represent a perfect situation. However, it is impossible to implant chronically a coronary arterial catheter large enough for the rapid injection necessary for satisfactory angiograms. Second, electrical pacing of the right atrium does not affect myocardial synergy, either while the animal is awake or while he is anesthetized with halothane (N. B. Ingels, Jr, G. T. Daughters, II, and N. T. Smith, unpublished observations). On the other hand, we wanted to maintain a constant heart rate, since end-diastolic volume is dependent upon this variable.[27]

## Significance of Results

In our attempt to provide a basis for a quantitative definition of myocardial synergy, it was assumed that, in order to perform optimally and generate adequate stroke volume and pressure during systole, the ventricle must:

1. *Shorten by Sufficient Amount to Eject Adequate Stroke Volume against Load.* This variable was expressed by mean shortening ($\bar{S}$), which is the average of the $S_{I,J}$ values for the six segments under study.

2. *Shorten Uniformly (that is, Isotropically).* Anisotropy (AI) was defined as the coefficient of variation of the six $S_{I,J}$ values. Although no ventricle is perfectly isotropic during contraction, efficient pumping demands that all circumferential segments are shortened by roughly the same amount during systole. Regional asyneresis, akinesis, and dyskinesis, in that order, will increase AI from control values.[21]

3. *Shorten Rapidly in Response to Excitation.* Mean time to half shortening ($\bar{T}_{50}$), the average of the $T_{50_{I,J}}$ values for the six segments, expresses the average velocity with which myocardial fibers contract once excited, and is related directly to systolic time intervals. Time to half shortening was picked as a typically well defined point of rapid linear dimensional change.

4. *Shorten Synchronously.* Asynchrony was defined as the coefficient of variation of the six $T_{50_{I,J}}$ values. A perfectly synchronous contraction would involve identical $T_{50}$'s for all segments under study. Although the intact ventricle would not be expected to be perfectly synchronous ($AS = 0$), near-synchronous behavior of all segments, that is, low values of AS, is crucial for efficient pumping.

To obtain a useful single value from these four variables, we developed the myocardial performance index (MPI). The MPI assumes that an increase in mean shortening is indicative of higher levels of myocardial performance and thus places $\bar{S}$ in the numerator of this expression. We further assumed that increased anisotropy, $\bar{T}_{50}$ and asynchrony indicate deteriorating myocardial performance and so place the sum of AI, $\bar{T}_{50}$, as AS in the denominator of the expression.

The index was constructed in this manner to emphasize the effect of shortening (approximately linear $\bar{S}$) and to minimize the effect of changes in heart rate (which influence $\bar{T}_{50}$), yet remain quite sensitive (approximately an exponential relationship) to changes in AI and AS. The variables $\bar{S}$, AI, $\bar{T}_{50}$, AS, and MPI are directly comparable from subject to subject when similar epicardial sites and projection angles are used, as was done in this study.

The uniqueness of the MPI lies not in its ability to act as another indicator of myocardial depression from anesthetic agents, but rather in its sensitivity in detecting myocardial dysfunction due to temporary or permanent ischemia. Much of the change in the MPI seen in these studies arises from the increase in one of the denominator factors, anisotropy. Much of the change which follows myocardial ischemia, on the other hand, comes from changes in asynchrony (N. B. Ingels, Jr., G. T. Daughters, II, N. T. Smith, unpublished observations). Thus the effect of halothane and ischemia can be separated by the present method, giving hope for a monitoring technique that could detect myocardial ischemia during anesthesia.

We can say, at least by our definitions, that one cannot detect in the dog any significant increase in anisotropy or asynchrony produced by *clinical concentrations* of halothane. This observation has two implications. First, little, if any, of the halothane-induced cardiac depression arises from changes in these two variables. Second, changes in measurements of intact cardiac performance, such as $dP/dt_{max}$, where $P$ = ventricular pressure, may be reasonably valid, provided that loading conditions are taken into account. On the other hand, some asynergy *is* present at all times, and the individual animal may show significant changes in it. Thus, measurements that base their validity on certain assumptions about homogeneity of structure and synchrony of contraction may be difficult to justify. These include $(dP/dt_{max})/KP$, as well as $V_{max}$ derived from plotting pressure against $(dP/dt_{max})/KP$, where $K$ = a constant and $V$ = myocardial fiber velocity.

With one exception, not included in these data, the hearts of these dogs were ostensibly normal. We do not know what impact halothane might have upon the heart with preexisting, significant asynergy. Information derived from the single animal with preexisting myocardial ischemia suggests that halothane may significantly increase dyscoordinate contraction (N. T. Smith, N. B. Ingels, Jr., G. T. Daughters II, and L. Wexler, unpublished observations).

### REFERENCES

1. Goldberg AH, Ullrick WC: Effects of halothane on isometric contractions of isolated heart muscle. Anesthesiology 28:838-845, 1967
2. Merin RG: Subcellular mechanisms for the negative inotropic effect of inhalation anesthetics, in Molecular Mechanisms of

Anesthesia. Edited by BR Fink (Progress in Anesthesiology, Vol 1). New York, Raven Press, 1975, pp 603-615

3. Berman MC, Kewley CF, Kench JE: Contribution of inhibition of NADH-dehydrogenase to the cardiotoxic effects of halothane. J Mol Cell Cardiol 6:39-48, 1974
4. Merin RG, Kumazawa T, Honig CR: Reversible interaction between halothane and $Ca^{++}$ on cardiac actomyosin adenosine triphosphate: mechanism and significance. J Pharmacol Exp Ther 190:1-14, 1974
5. Price HL: $Ca^{++}$ reverses myocardial depression caused by halothane: site of action. Anesthesiology 41:576-579, 1974
6. Ohnishi T, Pressman GS, Price HL: A possible mechanism of anesthetic-induced myocardial depression. Biochem Biophys Res Commun 57:316-322, 1974
7. Goldberg AH, Phear WPC: Alterations in mechanical properties of heart muscle produced by halothane. J Pharmacol Exp Ther 162:101-108, 1968
8. Smith NT, Smith PC: Circulatory effects of modern inhalation anesthetic agents, in Modern Inhalation Anesthetic Agents, Heffter's Handbook of Experimental Pharmacology, Vol 30, Edited by MB Chenoweth, Berlin, Springer Verlag, 1972, pp 149-241
9. Epstein RA, Wang HH, Bartelstone HJ: The effects of halothane on circulatory reflexes of the dog. Anesthesiology 29:867-876, 1968
10. Paradise RR, Ko KC: The effect of fructose on halothane-depressed rat atria. Anesthesiology 32:124-129, 1970
11. Price HL, Price ML: Has halothane a predominant circulatory action? Anesthesiology 27:764-769, 1966
12. Price HL, Price ML, Morse HT: Effects of cyclopropane, halothane, and procaine on the vasomotor "centre" of the dog. Anesthesiology 26:55-60, 1965
13. Etsten BE, Shimosato S: "Myocardial contractility": performance of the heart during anesthesia, in Anesthesia and the Circulation. Edited by L Fabian. Philadelphia, FA Davis Co, 1964, pp 55-78
14. Shimosato S, Li TH, Etsten B: Ventricular function during halothane anesthesia in closed chest dog. Circ Res 12:63-75, 1963
15. Prys-Roberts C, Gersh BJ, Baker AB, et al: The effects of halothane on the interactions between myocardial contractility, aortic impedance, and left ventricular performance. I. Theoretical considerations and results Br J Anaesth 44:634-649, 1972
16. Gersh BJ, Prys-Roberts C, Reuben SR, et al: The effects of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance. II. Aortic input impedance, and the distribution of energy during ventricular ejection. Br J Anaesth 44:767-775, 1972
17. Gersh B, Prys-Roberts C, Baker AB: The effects of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance. III: Influence of stimulation of sympathetic nerves, beta adrenergic receptors, and myocardial fibres. Br J Anaesth 44:995-1005, 1972
18. Eger EI II, Brandstater B, Saidman LJ, et al: Equipotent concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon, and nitrous oxide in the dog. Anesthesiology 26:771-777, 1965
19. Kong Y Morris JJ Jr, McIntosh HD: Assessment of regional myocardial performance from biplane coronary cineangiograms. Am J Cardiol 27:529-537, 1971
20. Ingels NB Jr, Daughters GT II: A quantitative definition of ventricular asynergy. Cardiovasc Res 8:632-639, 1974
21. Zaret BL Pitt B, Ross RS: Determination of the site, extent, and significance of regional ventricular dysfunction during acute myocardial infarction. Circulation 45:441-456, 1972
22. Daughters GT, Ingels NB Jr, Carrera CJ: Regional myocardial dynamics from a single-plane coronary cineangiograms. J Biomech 6:25-30, 1973
23. Harrison DC, Goldblatt A, Braunwald E: Studies on cardiac dimensions in intact, unanesthetized man. I. Description of techniques and their validation. Circ Res 13:448-467, 1963
24. Feigl EO, Fry DL: Intramural myocardial shear during the cardiac cycle. Circ Res 14:436-450, 1964
25. Streeter DD Jr, Spotnitz HM, Patel DP, et al: Fiber orientation in the canine left ventricle during diastole and systole. Circ Res 24:339-347, 1969
26. Ingels NB Jr, Daughters GT II, Davies SR, et al: Stereo photogrammetric studies on the dynamic geometry of the canine left ventricular epicardium. J Biomech 4:541-550, 1971
27. Bishop VS, Horwitz LD: Effects of altered autonomic control on left ventricular function in conscious dogs. Am J Physiol 221:1273-1282, 1971

ANESTH ANALG
59:186-191, 1980

# Aminophylline Pharmacokinetics and Cardiorespiratory Effects during Halothane Anesthesia in Experimental Animals

**Joseph A. Stirt, MD,* Jack M. Berger, MD, PhD,† Sandra M. Ricker, BS,‡ and Stuart F. Sullivan, MD§**

---

STIRT, J. A., BERGER, J. M., RICKER, S. M., AND SULLIVAN, S. F.: Aminophylline pharmacokinetics and cardiorespiratory effects during halothane anesthesia in experimental animals. Anesth Analg 59:186–191, 1980.

The pharmacokinetics and cardiorespiratory effects of aminophylline during halothane anesthesia are not well established and are the subject of this study. Eleven dogs were anesthetized with 1% halothane in air and given 10 mg/kg of intravenous aminophylline (theophylline ethylenediamine) over 5 minutes. Serum theophylline levels were measured over the next 60 minutes and were found to be in the therapeutic range (10–20 mg/L). Theophylline levels decayed according to a two-component exponential function. The half-time for the fast component was 4.5 minutes, while the slow component half-time was 134.5 minutes. Heart rate increased significantly ($p < 0.05$) within 2 minutes following aminophylline, and remained significantly elevated for 60 minutes. Pulmonary capillary wedge pressure and systemic vascular resistance decreased 2 minutes after aminophylline, as did the arterial-mixed venous oxygen content difference. Cardiac index increased 2 minutes following aminophylline. All these changes were transient, and values returned to near control values within 10 minutes after aminophylline. Arterial oxygenation, venous admixture, and physiologic dead space were not significantly ($p > 0.05$) altered by aminophylline. No cardiac arrhythmias occurred. Other than a sustained 12% increase in heart rate, and transient hemodynamic changes immediately following its administration, aminophylline in therapeutic doses did not have adverse effects on cardiorespiratory function during prolonged 1% halothane anesthesia in normoxic, eucapnic dogs.

**Key Words:** PHARMACOKINETICS: aminophylline; PHARMACOLOGY: aminophylline; ANESTHETICS, Volatile: halothane.

---

HALOTHANE is considered the inhalation anesthetic agent of choice for the asthmatic patient requiring surgery.[1-3] Whereas aminophylline (theophylline ethylenediamine) is commonly used in the treatment of asthma in the nonoperative setting, cardiac arrhythmias have been reported in patients receiving intravenous aminophylline and subsequently anesthetized with halothane.[4, 5] In addition, ventricular arrhythmias have been reported to occur in dogs given aminophylline during halothane anesthesia.[6-8]

Conflicting reports exist on the effect of aminophylline on arterial oxygenation in conscious man.[9-13] Its effects on other cardiorespiratory and hemodynamic parameters have also been reported in con-

---

* Resident and Research Fellow.

† Research Associate.

‡ Technical Services Supervisor.

§ Professor.

Supported by a grant from the UCLA Department of Anesthesiology.

Received from the Department of Anesthesiology, UCLA School of Medicine Los Angeles, California 90024.

Reprint requests to Dr. Stirt.

scious human subjects but never related to serum theophylline levels.[14-16] There seem to be no systematic studies of the cardiorespiratory effects of aminophylline during halothane anesthesia in which serum theophylline levels were determined.

This study was designed to investigate aminophylline pharmacokinetics and to quantify the cardiorespiratory and hemodynamic effects of aminophylline at measured serum theophylline concentrations during halothane anesthesia.

## Methods and Materials

Eleven adult mongrel dogs, weighing 18.5 to 26 kg (average 22.1 kg), were sedated with intravenous sodium pentobarbital, 30 mg/kg. Cuffed orotracheal tubes were inserted and an airtight fit secured. The orotracheal tube was connected to a Harvard animal respirator delivering 1% halothane in air at a rate of 12 breaths per minute. End-tidal carbon dioxide concentration was maintained at approximately 4.5% by adjusting tidal volume.

Exhaled gas was collected in a modified volume displacement spirometer (model 220 spirometer, Cardiopulmonary Instruments, Inc, Houston, TX). Gas analysis of inspired and mixed expired air was performed using a gas mass spectrometer (model MGA-1100, Perkin-Elmer Corp, Pomona, CA). Measurement of exhaled volume, gas analysis, and computation of oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were completed in real time at approximately 1-minute intervals using a comprehensive computer program run on a general purpose laboratory minicomputer system (Data General, Westboro, MA), details of which have been described previously.[17] Temperature measured with a thermistor placed in the lower third of the esophagus was maintained between 37–38 C throughout the study with a heating lamp and blanket. A continuous lead II electrocardiogram was recorded.

Mean arterial blood pressure (MAP) was measured using a femoral artery catheter connected to a pressure transducer (Bentley Trantec, Irvine, CA) and recorded. Mean pulmonary artery pressure ($\overline{PA}$) and pulmonary capillary wedge pressure (PCWP) were measured with a Swan-Ganz catheter placed via an external jugular vein, with pressure contours confirming location. A second catheter for blood sampling was placed in the right ventricle by the same method. An intravenous infusion of 0.9% NaCl at 100 ml/hr was begun and maintained for the duration of the study.

All animals were allowed to stabilize for at least 90 minutes following institution of controlled ventilation and halothane. When heart rate (HR), MAP, $\dot{V}_{O_2}$, and $\dot{V}_{CO_2}$ had been stable for at least 60 minutes, aminophylline (theophylline ethylenediamine, Invenex), 10 mg/kg, was infused intravenously over 5 minutes. Arterial blood samples were obtained from the femoral arterial catheter and mixed venous blood samples from the right ventricular catheter. All samples were collected in heparinized glass syringes and iced immediately. Blood oxygen tension ($P_{O_2}$), carbon dioxide tension ($P_{CO_2}$), and pH were measured in duplicate in all samples (model 313 blood gas analyzer, Instrumentation Laboratory, Inc, Boston, MA).

Arterial and mixed venous blood samples for measurement of $P_{O_2}$, $P_{CO_2}$, and pH were obtained 10 and 5 minutes before aminophylline administration, and 2, 5, 10, 15, 30, 45, and 60 minutes following injection of aminophylline. Corrections were made for the loss of oxygen in the iced sample during the interval before analysis and for oxygen electrode blood gas difference by tonometry. Hemoglobin (Hb) concentration was determined in duplicate by colorimetry in all arterial samples. The blood gas and hemoglobin data were used to calculate the alveolar-arterial oxygen difference ($A\text{-}aD_{O_2}$), arterial-mixed venous oxygen content difference ($C\bar{a}_{O_2}$-$C\bar{v}_{O_2}$), percentage of physiologic dead space ($V_D/V_T$), percentage of venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$), and respiratory exchange ratio (R). Serum theophylline levels were determined in duplicate in all arterial blood samples by homogenous enzyme immunoassay (EMIT, Syva, Palo Alto, CA), in which competitive protein binding was determined spectrophotometrically using a labeled enzyme and specific binding antibody.[18]

**ABBREVIATIONS**

| | |
|---|---|
| $P_{O_2}$ | blood oxygen tension (torr) |
| $P_{CO_2}$ | blood carbon dioxide tension (torr) |
| Hb | hemoglobin (mg/100 ml) |
| $\underline{MAP}$ | mean femoral artery blood pressure (torr) |
| $\overline{PA}$ | mean pulmonary artery blood pressure (torr) |
| PCWP | pulmonary capillary wedge pressure (torr) |
| HR | heart rate (beats/minute) |
| CI | cardiac index (L/min/m$^2$) |
| SVR | systemic vascular resistance (dynes·sec·cm$^{-5}$) |
| $Ca_{O_2}$-$C\bar{v}_{O_2}$ | arterial-mixed venous oxygen content difference (ml%) |
| $\dot{V}_{CO_2}$ | carbon dioxide production (ml/min/m$^2$) |
| $\dot{V}_{O_2}$ | oxygen consumption (ml/min/m$^2$) |
| R | respiratory exchange ratio |
| $A\text{-}aD_{O_2}$ | alveolar-arterial oxygen difference (torr) |
| $V_D/V_T$ | physiologic dead space (%) |
| $\dot{Q}_{VA}/\dot{Q}_T$ | venous admixture (%) |

All animals served as their own control. Data were analyzed by paired *t*-test, and values reported are means ± standard error.

## Results

Serum theophylline levels are listed in Table 1 and graphically depicted in Fig 1. Mean theophylline levels decayed according to a two-component (alpha and beta) exponential function described by the equation $C = 9.5e^{-0.1487t} + 12.6e^{-0.00515t}$, where C represents the serum theophylline concentration at time "t" after aminophylline administration. The calculated half-time for alpha was 4.5 minutes, while the half-time for the beta phase was 134.5 minutes.

No arrhythmias occurred in any animal at any time during the study. All functions that changed significantly following aminophylline are listed in Tables 1 and 2 and are shown graphically in Figs 2 and 3. Heart rate increased significantly ($p < 0.05$) following aminophylline from 131 ± 7 to 147 ± 5 beats/minute (12% increase) and remained significantly elevated for the duration of the study. Pulmonary capillary wedge pressure significantly ($p < 0.05$) decreased only at 2 minutes following aminophylline, from 9 ± 1 to 5 ± 1 torr. Systemic vascular resistance (SVR) decreased in the first 2 minutes following aminophylline from 2396 ± 262 to 2139 ± 246 dynes·sec·cm$^{-5}$ ($p < 0.05$), remained low for approximately 5 minutes after aminophylline, and then gradually returned to near control values. Cardiac index (CI) increased within 2 minutes following aminophylline from 3.51 ± 0.28 to 3.73 ± 0.24 L/min/m$^2$ ($p < 0.05$), remaining elevated until 10 minutes following aminophylline, when it also returned to near control values. Arterial-mixed venous oxygen content difference fell from 3.5 ± 0.2 to 3.2 ± 0.2 ml% ($p < 0.05$) 2 minutes following aminophylline.

Control MAP was 91.7 ± 7.2 torr. Control arterial $P_{O_2}$, $P_{CO_2}$, and pH were 82.3 ± 1.8 torr, 33.7 ± 0.9 torr, and 7.35 ± 0.01, respectively. Control values for $V_D/V_T$ and $\dot{Q}_{VA}/\dot{Q}_T$ were 48.4 ± 2.3% and 19.4 ± 1.7%, respectively. No significant changes ($p > 0.05$) were noted in any of these values during the course of the experiment (Tables 1 and 2).

Control values of other cardiorespiratory functions

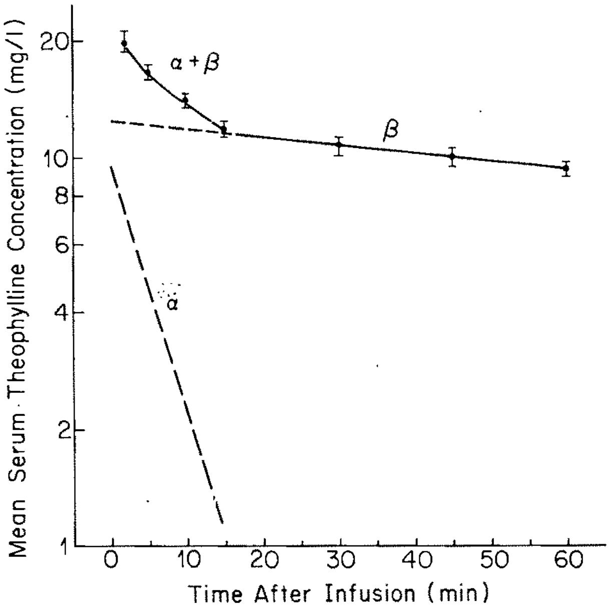


FIG 1. Semilogarithmic plot of average (±SE) serum theophylline concentrations versus time in 11 dogs after aminophylline, 10 mg/kg IV. The slope of the decay curve is given by $C = 9.5e^{-0.1487t} + 12.6e^{-0.00515t}$, where C represents serum theophylline concentration at time "t" in minutes. The decay curve consists of two components, $\alpha(t_{1/2} = 4.5$ minutes) and $\beta(t_{1/2} = 134.5$ minutes). Correlation coefficient = −0.996.

**TABLE 1**

**Hemodynamic Functions following 10 mg/kg of Aminophylline***

| Time after control | Serum theophylline | Heart rate | Pulmonary capillary wedge pressure | Systemic vascular resistance | Cardiac index | Mean arterial pressure |
|---|---|---|---|---|---|---|
| *min* | *mg/L* | *beats/min* | *torr* | *dynes·sec·cm$^{-5}$* | *L/min/m$^2$* | *torr* |
| Control | 0 | 131 ± 7 | 9 ± 1 | 2396 ± 262 | 3.51 ± 0.28 | 92 ± 7 |
| 2 | 19.8 ± 0.9 | 147 ± 5† | 5 ± 1† | 2139 ± 246† | 3.73 ± 0.24† | 87 ± 7 |
| 5 | 16.8 ± 0.7 | 147 ± 5† | 6 ± 1 | 2255 ± 288† | 3.70 ± 0.27† | 88 ± 7 |
| 10 | 14.2 ± 0.5 | 147 ± 4† | 6 ± 1 | 2401 ± 307 | 3.49 ± 0.29 | 87 ± 7 |
| 15 | 11.9 ± 0.5 | 146 ± 4† | 6 ± 1 | 2383 ± 339 | 3.55 ± 0.28 | 87 ± 8 |
| 30 | 10.8 ± 0.6 | 142 ± 4† | 7 ± 1 | 2411 ± 289 | 3.32 ± 0.22 | 87 ± 7 |
| 45 | 10.1 ± 0.6 | 144 ± 4† | 8 ± 1 | 2506 ± 278 | 3.23 ± 0.17 | 90 ± 6 |
| 60 | 9.4 ± 0.4 | 146 ± 5† | 7 ± 1 | 2698 ± 307 | 3.19 ± 0.21 | 93 ± 6 |

* Values are means ± SEM.

† $p < 0.05$.

**TABLE 2**

**Respiratory Functions following 10 mg/kg of Aminophylline***

| Time after control | Serum theophylline | Arterial-mixed venous oxygen content difference | Arterial $P_{O_2}$ | Arterial $P_{CO_2}$ | Arterial pH | Physiologic dead space | Venous admixture |
|---|---|---|---|---|---|---|---|
| *min* | *mg/L* | *ml %* | *torr* | *torr* | | % | % |
| Control | 0 | 3.5 ± 0.2 | 82.3 ± 1.8 | 33.7 ± 0.9 | 7.35 ± 0.01 | 48.4 ± 2.3 | 19.4 ± 1.7 |
| 2 | 19.8 ± 0.9 | 3.2 ± 0.1† | 83.2 ± 1.9 | 33.4 ± 0.7 | 7.35 ± 0.01 | 49.4 ± 1.8 | 20.5 ± 2.1 |
| 5 | 16.8 ± 0.7 | 3.6 ± 0.2 | 82.4 ± 1.9 | 33.8 ± 1.0 | 7.35 ± 0.01 | 50.3 ± 1.9 | 20.6 ± 2.2 |
| 10 | 14.2 ± 0.5 | 3.7 ± 0.2 | 81.8 ± 1.7 | 32.7 ± 0.9 | 7.35 ± 0.01 | 48.6 ± 2.2 | 20.5 ± 1.9 |
| 15 | 11.9 ± 0.5 | 3.6 ± 0.3 | 81.0 ± 2.0 | 33.0 ± 1.0 | 7.35 ± 0.01 | 48.9 ± 1.8 | 21.6 ± 2.2 |
| 30 | 10.8 ± 0.6 | 3.8 ± 0.2 | 82.2 ± 1.7 | 33.5 ± 1.1 | 7.34 ± 0.01 | 48.9 ± 2.1 | 19.5 ± 1.7 |
| 45 | 10.1 ± 0.6 | 4.0 ± 0.1 | 82.8 ± 1.8 | 33.8 ± 1.0 | 7.34 ± 0.01 | 48.5 ± 1.7 | 19.1 ± 1.7 |
| 60 | 9.4 ± 0.4 | 4.0 ± 0.1 | 82.7 ± 2.0 | 33.9 ± 1.1 | 7.33 ± 0.01 | 48.1 ± 1.8 | 19.0 ± 1.9 |

* Values are means ± SEM.
† $p < 0.05$.

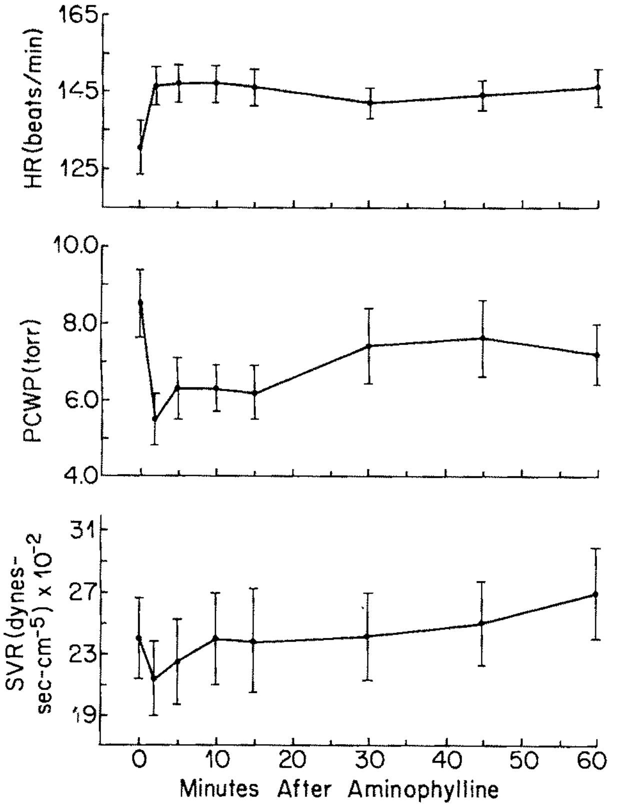


FIG 2. Heart rate (HR), pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR) as a function of time after aminophylline, 10 mg/kg. All points represent means ±SE for 11 animals.

that did not change significantly ($p > 0.05$) following aminophylline included $\overline{PA}$ (14.4 ± 1.3 torr), pulmonary vascular resistance (191 ± 38 dynes·sec·cm$^{-5}$), mixed venous $P_{O_2}$, $P_{CO_2}$, and pH (46.4 ± 1.3 torr, 36.0 ± 1.3 torr, and 7.33 ± 0.01, respectively), and R (0.89 ± 0.01). Others included A-$a_{DO_2}$ (28.5 ± 2.1 torr), $\dot{V}_{CO_2}$ (108 ± 6.3 ml/min/m$^2$), $\dot{V}_{O_2}$ (121.4 ± 6.2 ml/min/m$^2$), and Hb (14.0 ± 0.6 mg/100 ml).

## Discussion

Two aspects of the pharmacologic actions of aminophylline deserve attention: direct effects on myocardial activity and general systemic smooth muscle effects. Serious arrhythmogenic effects of intravenous aminophylline were first reported in 1943.[19] Subsequent clinical reports[20-23] have added to the impression that aminophylline can produce severe ventricular arrhythmias and cardiac arrest. Canine studies[24] have documented a significant reduction in ventricular fibrillatory threshold with aminophylline.

Several studies[6-8] have found aminophylline to be a potent arrhythmogenic agent in the presence of halothane. These studies utilized large boluses of intravenous aminophylline, but provided no serum theophylline levels at the time arrhythmias occurred. Instances of ventricular arrhythmias during halothane anesthesia in patients who had previously received aminophylline have been reported.[4,5] Serum theophylline values during occurrence of those arrhythmias were not reported either.

In our study a 5-minute infusion of aminophylline, 10 mg/kg, was given after at least 90 minutes of constant 1% halothane anesthesia during which time HR, MAP, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ had been stable for at least 60 minutes prior to the infusion. Theophylline levels were measured throughout the study and decreased from a mean peak level of 19.8 ± 0.9 mg/ml 2 minutes following completion of the infusion to 9.4 ± 0.4 mg/ml at 60 minutes. A bolus injection would have produced a higher peak level.

The blood level of theophylline fell exponentially

ANESTH ANALG
59:192–196, 1980

# Gas Viscosity Effects in Anesthesia

C. S. Jones, MB, ChB

JONES, C. S.: Gas viscosity effects in anesthesia. Anesth Analg 59:192–196, 1980.

The viscosity effects when carrier anesthetic gases are passed through ventilators can lead to significant alterations in ventilating volumes. This effect was studied in both experimental and clinical situations using the Bird anesthetic machine powered by a nitrous oxide-oxygen blender and fitted with a Wright gas-volume meter. Despite the fact that nitrous oxide is ± 30% denser than oxygen, when it is used as the main carrier gas through the Bird anesthetic machine during automatic ventilation, the ventilating volumes increase although the settings on the machine remain unaltered. When the machine is slave to the spontaneous respiratory efforts of the patient this effect disappears. Oxygen is more viscous than nitrous oxide and this will explain the observed phenomena. It is suggested that it would be safer for patients if vaporizers and ventilators were calibrated with a 3:1 mixture of nitrous oxide and oxygen.

**Key Words:** PHYSICS: viscosity; EQUIPMENT: viscosity; OXYGEN: viscosity; ANESTHETICS, Gases: nitrous oxide.

THE fact that the composition of the gas flowing through a temperature-compensated, calibrated vaporizer may influence the delivered concentration of the anesthetic vapor has been discussed by Nawaf and Stoelting.[1] Output of enflurane from Ēthrane vaporizers at given calibration settings appeared greater when nitrous oxide formed part of the carrier gas than when oxygen alone was used. Nawaf and Stoelting[1] speculate that the altered density of the carrier gas induces a "back pressure" that must be overcome before flow into the vaporizing chamber can occur because the denser nitrous oxide increases the resistance to flow.

Using the Bird anesthetic machine we have tested their speculations indirectly by measuring the volume flow of carrier gas per unit of time during (1) experimental circumstances and (2) clinical anesthesia.

## Methods

The prototype Bird anesthetic machine[2] is a Mark 14 positive-phase ventilator powered via a $N_2O$-$O_2$ blender. The composition of the carrier gas can be altered rapidly in the range $N_2O$ nil and $O_2$ 100% to $N_2O$ 75% and $O_2$ 25%. A vaporizer and a Wright ventilation meter are inserted into the patient delivery line.

In the experiments the vaporizer was switched off and the distally situated Bird Glengary exhalation valve, which forms the connection between the system and the patient, was attached directly to an 8-mm i.d., armored latex endotracheal tube 22 cm long. The inspiratory triggering pressure was set at the 5-mm mark and the cut-off (maximum inflation) pressure was set at 10 mm. The controls regulating the triggering rate and the rate of inflation were set at the marks indicating average normal values. The machine now cycled automatically against the resistance offered by the endotracheal tube.

The carrier gas composition was selected by rotating the control dial, and the Wright ventilation meter was turned off and set at zero. After allowing the machine to cycle several times, the Wright meter was turned on just after the completion of a cycle, and a stopwatch synchronously started. The number of cycles was counted and at the end of 1 minute the Wright meter was turned off. The volume of carrier gas passed through the system could now be read and recorded. After altering the composition of the carrier gas by rotating the control valve, the whole operation was repeated.

During clinical anesthesia the circumstances of the experiment remained the same, except that attached in train to the Glengary valve, was a patient. Here the vaporizer was in circuit and the dictates of the type of surgery, as well as the anatomical and physiologic make-up of the patient, determined the settings on the Bird machine which controlled the rate, the vol-

---

Received from 314 Sanlam Building, Worcester, Republic of South Africa. Accepted for publication October 29, 1979.

ume, and the pressure required to ventilate the patient adequately. These settings varied from patient to patient but, except for the nature of the carrier gas, were *not* changed during the period of an individual measurement.

## Results

In a series of 22 experimental operations, during which the machine cycled continuously and the only alteration made to the system was the change back and forth between 100% $O_2$ (11 runs) and 75% $N_2O$ and 25% $O_2$ (11 runs), the mean volume of $O_2$ delivered was 9,267 ± 465 ml (5%) per minute and the mean volume of 75% $N_2O$ and 25% $O_2$ delivered was 12,199 ± 206 ml (1.7%) per minute. That is to say, when all parameters of the system, except the composition of the carrier gas, remained unchanged, the volume of the nitrous oxide-rich gas delivered in unit time was 31% greater than that of oxygen alone. These results are listed in Table 1.

When a fixed number of cycles (30) was timed and the volume delivered was measured, in a typical experiment 22.0 L of oxygen were delivered in 2 minutes 34 seconds, while 27.7 L of the $N_2O$ 75% and 25% $O_2$ mixture were delivered in 2 minutes 19 seconds. Expressed in milliliters per *second, there* is an increase of 39% in volume flow when nitrous oxide is the main carrier gas.

**TABLE 1**

**Experimental Results***

| Run no. | Carrier gas composition | No. of cycles/min | Volumes of gas delivered | Difference in volumes | % of difference |
|---|---|---|---|---|---|
| | | | *ml* | *ml* | |
| 1 | $O_2$ | 11 | 9,200 | +3,150 | +34% |
| | $N_2O$-$O_2$ | 13 | 12,350 | | |
| 2 | $O_2$ | 12 | 9,650 | +2,750 | +28% |
| | $N_2O$-$O_2$ | 13 | 12,400 | | |
| 3 | $O_2$ | 12 | 9,920 | +2,420 | +24% |
| | $N_2O$-$O_2$ | 13 | 12,340 | | |
| 4 | $O_2$ | 12 | 9,900 | +2,510 | +25% |
| | $N_2O$-$O_2$ | 13 | 12,410 | | |
| 5 | $O_2$ | 11 | 9,200 | +3,000 | +33% |
| | $N_2O$-$O_2$ | 13 | 12,200 | | |
| 6 | $O_2$ | 11 | 9,190 | +3,050 | +33% |
| | $N_2O$-$O_2$ | 13 | 12,240 | | |
| 7 | $O_2$ | 11 | 9,170 | +3,080 | +33% |
| | $N_2O$-$O_2$ | 13 | 12,250 | | |
| 8 | $O_2$ | 11 | 8,200 | +4,010 | +49% |
| | $N_2O$-$O_2$ | 13 | 12,210 | | |
| 9 | $O_2$ | 11 | 9,180 | +2,960 | +32% |
| | $N_2O$-$O_2$ | 13 | 12,140 | | |
| 10 | $O_2$ | 11 | 9,180 | +2,570 | +28% |
| | $N_2O$-$O_2$ | 13 | 11,750 | | |
| 11 | $O_2$ | 11 | 9,150 | +2,750 | +30% |
| | $N_2O$-$O_2$ | 13 | 11,900 | | |

* Mean volume of oxygen per experiment: 9,267 ± 465 ml (±5%); mean volume of nitrous oxide-$O_2$ per experiment: 12,199 ± 206 ml (±1.7%); difference in volumes: 2,932 ml, i.e., 31.6% increase.

The results of 34 determinations on 14 patients (Table 2) show that when the composition of the carrier gas is largely nitrous oxide, a greater volume is regularly delivered in unit time. The actual pooled totals (1,913.95 L of oxygen and 2,541.40 L of 75% nitrous oxide and 25% oxygen) again show an increase of the magnitude of 32% when nitrous oxide is a major part of the carrier gas.

The Bird machine will also operate as slave to the patient's own respiratory efforts and in Table 3 are shown 15 control measurements from eight patients (seven of these patients are included in Table 2 also). The pooled totals again show a difference of 48.80 L between oxygen only and the nitrous oxide-oxygen mixture, but this is now only 4.2%, a difference that is within the range of experimental error as determined in Table 1. The marked alteration related to carrier gas composition has disappeared. Moreover the differences are no longer all in the same direction. In five of the 15 measurements the direction of change is opposite that of the remaining 10.

## Discussion

This is not a highly precise study of absolute values but a comparative study of the degree and direction of change in a single dependent variable (ventilating volume) when an independent variable (ventilating gas composition) is altered, while all other parameters are held constant. The volume meter used for the measurements was not specially calibrated. It has been assumed that faults or imprecisions in the meter remain constant and that errors were always in the same direction during the course of the study. The meter has been used as one would use a randomly selected stick to measure roughly the distance between objects in order to confirm a subjective estimate of their spatial relationship.

Readings of the meter were made by naked eye and to the nearest 10 ml. The viscosity effect may well introduce an error in the performance of this meter but the surface area of the vanes of the meter is so small in comparison to the total surface area of the system, and the volumes measured so large, that this possible error has not been explored.

Other sources of error to be considered are fluctuations in the line pressures of the piped gas-supplies which power the Bird; variations within the Bird due

**TABLE 2**

**Clinical Results during Controlled Ventilation**

| Patient | Carrier gas composition | % halothane | No. of cycles/min | Inflation pressure settings | Volumes of gas | Difference in gas volumes |
|---|---|---|---|---|---|---|
| | | | | *mm Hg* | *ml* | *ml* |
| A.B. | $O_2$ | 0.75 | 9 | 18 | 4,900 | +2,750 |
| | $N_2O$-$O_2$ | | 9 | 18 | 7,650 | |
| J.C | $O_2$ | 0.75 | 8 | 15 | 5,880 | +320 |
| | $N_2O$-$O_2$ | | 8 | 15 | 6,200 | |
| | $O_2$ | 0.75 | 8 | 15 | 4,700 | +1,100 |
| | $N_2O$-$O_2$ | | 8 | 15 | 5,800 | |
| | $O_2$ | 0.75 | 8 | 15 | 4,800 | +1,240 |
| | $N_2O$-$O_2$ | | 8 | 15 | 6,040 | |
| | $O_2$ | 0.75 | 8 | 15 | 5,240 | +2,560 |
| | $N_2O$-$O_2$ | | 8 | 15 | 7,800 | |
| J.R. | $O_2$ | 0.50 | 13 | 15 | 9,040 | +2,360 |
| | $N_2O$-$O_2$ | | 13 | 15 | 11,400 | |
| | $O_2$ | 0.50 | 13 | 10 | 5,740 | +1,700 |
| | $N_2O$-$O_2$ | | 15 | 10 | 7,440 | |
| | $O_2$ | 0.50 | 15 | 10 | 5,920 | +2,930 |
| | $N_2O$-$O_2$ | | 16 | 10 | 8,850 | |
| | $O_2$ | 0.50 | 14 | 10 | 5,360 | +1,890 |
| | $N_2O$-$O_2$ | | 15 | 10 | 7,250 | |
| C.C. | $O_2$ | 0.75 | 8 | 15 | 5,350 | +850 |
| | $N_2O$-$O_2$ | | 8 | 15 | 6;200 | |
| | $O_2$ | 0.75 | 8 | 15 | 4,590 | +1,130 |
| | $N_2O$-$O_2$ | | 8 | 15 | 5,720 | |
| | $O_2$ | 1.0 | 7 | 15 | 4,080 | +1,850 |
| | $N_2O$-$O_2$ | | 8 | 15 | 5,930 | |
| S.LeR. | $O_2$ | 0.75 | 9 | 15 | 6,080 | +2,040 |
| | $N_2O$-$O_2$ | | 9 | 15 | 8,120 | |
| | $O_2$ | 0.75 | 9 | 15 | 6,080 | +1,840 |
| | $N_2O$-$O_2$ | | 9 | 15 | 7,920 | |
| | $O_2$ | 0.75 | 9 | 15 | 5,880 | +1,940 |
| | $N_2O$-$O_2$ | | 9 | 15 | 7,820 | |
| | $O_2$ | 0.75 | 9 | 15 | 6,100 | +1,850 |
| | $N_2O$-$O_2$ | | 9 | 15 | 7,950 | |
| C.G. | $O_2$ | 0.75 | 8 | 20 | 5,000 | +1,590 |
| | $N_2O$-$O_2$ | | 9 | 20 | 6,590 | |
| | $O_2$ | 1.0 | 8 | 20 | 4,960 | +1,960 |
| | $N_2O$-$O_2$ | | 8 | 20 | 6,920 | |
| | $O_2$ | 1.0 | 8 | 20 | 5,050 | +2,000 |
| | $N_2O$-$O_2$ | | 8 | 20 | 7,050 | |
| | $O_2$ | 1.0 | 8 | 20 | 5,000 | +2,200 |
| | $N_2O$-$O_2$ | | 8 | 20 | 7,200 | |
| M.dW. | $O_2$ | 0.75 | 8 | 15 | 4,300 | +780 |
| | $N_2O$-$O_2$ | | 8 | 15 | 5,080 | |
| | $O_2$ | 0.75 | 7 | 15 | 3,100 | +1,400 |
| | $N_2O$-$O_2$ | | 8 | 15 | 4,500 | |
| Z.vW. | $O_2$ | 0.75 | 9 | 15 | 5,640 | +2,900 |
| | $N_2O$-$O_2$ | | 10 | 15 | 8,540 | |
| | $O_2$ | 0.75 | 10 | 15 | 5,400 | +2,310 |
| | $N_2O$-$O_2$ | | 10 | 15 | 7,710 | |
| | $O_2$ | 0.75 | 10 | 15 | 5,560 | +1,640 |
| | $N_2O$-$O_2$ | | 10 | 15 | 7,200 | |
| J.V. | $O_2$ | 0.75 | 12 | 15 | 7,350 | +1,400 |
| | $N_2O$-$O_2$ | | 13 | 15 | 8,750 | |
| | $O_2$ | 0.75 | 12 | 15 | 7,300 | +1,300 |
| | $N_2O$-$O_2$ | | 12 | 15 | 8,600 | |
| | $O_2$ | 0.75 | 12 | 15 | 7,120 | +1,500 |
| | $N_2O$-$O_2$ | | 13 | 15 | 8,620 | |
| | $O_2$ | 0.75 | 12 | 15 | 7,110 | +1,740 |
| | $N_2O$-$O_2$ | | 13 | 15 | 8,850 | |
| L.B. | $O_2$ | 1.50 | 11 | 12 | 5,310 | +2,340 |
| | $N_2O$-$O_2$ | | 13 | 12 | 7,650 | |
| | $O_2$ | 1.0 | 10 | 15 | 7,750 | +3,450 |
| | $N_2O$-$O_2$ | | 9 | 15 | 11,200 | |
| | $O_2$ | 1.0 | 10 | 15 | 8,080 | +2,470 |
| | $N_2O$-$O_2$ | | 9 | 15 | 10,550 | |
| S.L. | $O_2$ | 0.75 | 9 | 15 | 4,200 | +1,800 |
| | $N_2O$-$O_2$ | | 9 | 15 | 6,000 | |
| | $O_2$ | 0.75 | 9 | 15 | 3,425 | +1,625 |
| | $N_2O$-$O_2$ | | 9 | 15 | 5,050 | |

to the differing densities and viscosities of the carrier gases; gas leaks within the Bird and the vaporizer; and alterations in the resistance to inflation offered by the patient.

Any leaks and variations in performance in the Bird ventilator due to altered carrier gas characteristics have been neglected because they occurred proximal to the Wright volume meter. Random checks of the pipe line pressures showed these to remain approximately stable at 40.4 Kpa (60 lb sq in) for each gas.

Leakages past the concentration control spindle of the Fluotec vaporizer are known to occur. They vary directly with the concentration setting and with the inflation pressures across the vaporizer but as they are also proximal to the Wright volume meter they have also been neglected. They are not a factor in the experimental series in Table 1.

Resistance to inflation distal to the Bird Glengary exhalation valve remained constant under the experimental conditions when the valve was connected directly to an 8.0-mm i.d. 22.0-cm long nylon-reinforced latex endotracheal tube. But when the resistance was a patient rendered apneic, either by overventilation or by curarization, other variables entered

**TABLE 3**
**Clinical Results during Spontaneous Respiration**

| Patient | Carrier gas composition | % halothane | Inflation pressure setting | Respiratory rate | Volumes of gas | Difference in volumes |
|---|---|---|---|---|---|---|
| | | | *mm Hg* | */min* | *ml* | *ml* |
| J.C. | $O_2$ | 0.75 | 10 | 10 | 5,600 | +220 |
| | $N_2O$-$O_2$ | | 10 | 10 | 5,820 | |
| J.R. | $O_2$ | 0.5 | 10 | 12 | 5,020 | +700 |
| | $N_2O$-$O_2$ | | 10 | 12 | 5,720 | |
| | $O_2$ | Nil | 10 | 21 | 8,010 | +580 |
| | $N_2O$-$O_2$ | | 10 | 19 | 8,590 | |
| C.C. | $O_2$ | 0.5 | 10 | 19 | 5,250 | +1,550 |
| | $N_2O$-$O_2$ | | 10 | 22 | 6,800 | |
| S.LeR. | $O_2$ | 0.75 | 10 | 8 | 3,620 | −120 |
| | $N_2O$-$O_2$ | | 10 | 8 | 3,500 | |
| C.G. | $O_2$ | 0.5 | 10 | 34 | 9,400 | +310 |
| | $N_2O$-$O_2$ | | 10 | 31 | 9,710 | |
| Z.vW. | $O_2$ | 1.5 | 10 | 20 | 8,900 | −830 |
| | $N_2O$-$O_2$ | | 10 | 18 | 8,070 | |
| | $O_2$ | 1.5 | 10 | 20 | 7,510 | +670 |
| | $N_2O$-$O_2$ | | 10 | 18 | 8,180 | |
| A.O. | $O_2$ | 0.75 | 10 | 29 | 8,580 | +1,620 |
| | $N_2O$-$O_2$ | | 10 | 27 | 10,200 | |
| | $O_2$ | 0.75 | 10 | 31 | 9,220 | +180 |
| | $N_2O$-$O_2$ | | 10 | 29 | 9,400 | |
| | $O_2$ | 0.75 | 10 | 30 | 9,080 | +80 |
| | $N_2O$-$O_2$ | | 10 | 28 | 9,160 | |
| | $O_2$ | 1.0 | 10 | 30 | 9,900 | −200 |
| | $N_2O$-$O_2$ | | 10 | 27 | 9,700 | |
| | $O_2$ | 1.0 | 10 | 31 | 9,910 | −500 |
| | $N_2O$-$O_2$ | | 10 | 27 | 9,410 | |
| | $O_2$ | 1.0 | 10 | 27 | 8,820 | +740 |
| | $N_2O$-$O_2$ | | 10 | 28 | 9,560 | |
| S.L. | $O_2$ | 0.75 | 10 | 23 | 6,960 | −140 |
| | $N_2O$-$O_2$ | | 10 | 23 | 6,820 | |

the equation. The anatomy and physiology of the patient's airways and lungs, the depth of anesthesia, the nature of the surgery, and the inflation pressures vary from patient to patient and no attempt was made to measure differences between patients. To reduce the effects of these variables to a minimum in individual patients, measurements were made over a short time span (1 minute) and any series was completed as quickly as possible.

Because of the existence of so many recognizable sources of error, no formal statistical analysis is made of the results obtained in the *clinical* situation. Here all volumes are pooled and a mean used to calculate the difference in ventilating volumes between the two carrier gases. The concern is to demonstrate the direction and approximate magnitude of any change, not to explore interpatient differences. Where viscosity is the decisive factor (i.e., in ventilated patients) the change is always in the same direction.

If, as Nawaf and Stoelting speculate, gas density is the property responsible for carrier gas-dependent changes in vapor concentrations delivered by modern vaporizers, one would not expect ventilating volumes to change so markedly and in the apparently wrong direction during automatic ventilation when similar carrier gas alterations occur, nor would one expect this effect to disappear during spontaneous respiration.

Nitrous oxide has a molecular weight of 44 and oxygen 32 (to the nearest whole number), a difference of 37.5% if oxygen is taken as the standard. The densities of the two gases are, respectively, 1,977 and 1,429 g/L at 0 C. Here the difference is 39.7%, again using oxygen as the standard. But if we look at the viscosity of the two gases the position is reversed.

Viscosity and density, as Table 4 demonstrates, are unrelated physical properties. The relationship between the viscosity of a gas and its temperature is linear in the temperature range 0–150 C and the curves expressing this relationship for nitrous oxide and for oxygen are parallel but widely separated. At 25 C the viscosity of oxygen, unlike its density, is considerably greater than that of nitrous oxide. Curiously this difference is also of the order of 39%, this time using nitrous oxide, the less viscous gas, as the standard. All these differences in magnitude of the various physical properties of the two gases accord with the vapor concentration differences detected by Nawaf and Stoelting but only viscosity can be seen to satisfy their observations and the observations reported here.

At any given pressure gradient across a vaporizing chamber molecules entering the gaseous phase from the liquid can interpenetrate a less viscous gas more readily and hence in greater abundance in a given time. Likewise, with a given resistance to ventilation, either human or purely physical, a greater volume of less viscous gas can be delivered in units of time when all other factors remain constant. But when the patient is breathing spontaneously across the vaporizer and triggering the assisting drive of the ventilator, the

**TABLE 4**
**Viscosity and Density***

| Substance | Viscosity | Density |
|---|---|---|
| | *centipoise* | *g/cm$^3$* |
| Mercury | 1.615 | 13.5704 |
| Water | 1.307 | 0.9997 |
| Olive oil | 138.0 | 0.9180 |

* All values at 10 C. Data from Weast.[3]

pressure gradient across the vaporizer is markedly increased, and changes in ventilation are dictated by the patient. Viscosity effects on ventilation become less significant, although an enrichment effect within the vaporizer may remain. If so, it would seem proper, in future, to use a 3:1 mixture of nitrous oxide and oxygen as the carrier gas when calibrating anaesthetic vaporizers. Inevitable variations in concentration, consequent on alterations of the composition of the gas administered to the patient through the vaporizer, will then be in the direction of greater safety to the patient.

### REFERENCES

1. Nawaf K, Stoelting RK: Nitrous oxide increases enflurane concentrations delivered by Ēthrane vaporizers. Anesth Analg 58:30-32, 1979
2. Jones CS: Modification of a Bird® Mark-14 anesthesia ventilator for greater versatility. Anesth Analg 55:879, 1976
3. Handbook of Chemistry and Physics. 59th Edition. (Edited by RC Weast. West Palm Beach, FL, CRC Press, 1978-1979

---

## Furosemide Affects Propranolol Activity

Although propranolol and furosemide are used together in the treatment of hypertension, the effects of furosemide on the plasma levels and beta blocking action of propranolol are not known. Ten healthy subjects were given propranolol, 40 mg orally. The mean plasma propranolol levels 60, 90, 180, and 300 minutes later were 85 ± 16, 90 ± 7, 82 ± 8, and 58 ± 8 ng/ml. Propranolol was then given together with furosemide (25 mg orally) and the propranolol blood levels were measured. Mean propranolol plasma levels were 106 ± 11 ng/ml at 60 minutes; 120 ± 12 ng/ml at 90 minutes ($p < 0.001$); 102 ± 9 ng/ml at 180 minutes ($p < 0.05$); and 78 ± 8 ng/ml at 300 minutes ($p < 0.01$). Six additional subjects were given an infusion of 1 μg/min of isoproterenol, increased by 0.5 μg/min until the heart rate increased by 25%, after oral administration of furosemide, 25 mg. This procedure was repeated after propranolol (40 mg orally) alone and after propranolol with furosemide (25 mg orally). The amount of isoproterenol that increased the heart rate by 25% was 2.6 ± 0.3 μg after furosemide alone and 17.7 ± 2 μg after propranolol ($p < 0.01$). After propranolol with furosemide the dose of isoproterenol required to increase heart rate by 25% was 109 ± 15 μg ($p < 0.001$). *(Chiariello M, Volpe M, Rengo F, et al: Effect of furosemide on plasma concentration and β-blockade by propranolol. Clin Pharmacol Ther 26:433-436, 1979)*

ANESTH ANALG
59:197-202, 1980

# Tracheobronchial Cytologic Changes and Abnormal Serum Electrophoretic Pattern during Induced Hypotension

**J. Barry O'Meara, MD,* Jack Chalon, MD,† Mahnoosh Amirdivani, MD,‡ Mahgul Ali, MD,* Mansoor Day, MD,§ and Herman Turndorf, MD||**

---

O'MEARA, J. B., CHALON, J., AMIRDIVANI, M., ALI, M., DAY, M., AND TURNDORF, H.: Tracheobronchial cytologic changes and abnormal serum electrophoretic pattern during induced hypotension. Anesth Analg 59:197–202, 1980.

Significantly increased numbers of iron-laden histiocytes are found in the airways of patients in hemorrhagic shock. Hemoglobin and products of its degradation bound to serum proteins can be identified by electrophoresis. Our concern about the use of halothane and positive pressure ventilation to provide controlled hypotension led us to study the numbers of iron-laden histiocytes associated with this and other methods used to achieve hypotension. Forty-three patients were studied. Profound hypotension (BP 50 torr or below) was induced in 10 patients and moderate hypotension (BP 60 torr) was induced in six patients using halothane and positive pressure breathing. In addition, moderate hypotension was achieved using: sodium nitroprusside (with $N_2O$-halothane in six patients and with $N_2O$-narcotic in six patients), and trimethaphan (with $N_2O$-halothane in six patients and with $N_2O$-narcotic in nine patients). Tracheobronchial secretions obtained at the onset and termination of hypotension were stained with Prussian blue, and the percentage of iron-laden histiocytes was determined in a minimum of 400 cells. Haptoproteins in serum specimens obtained simultaneously were measured by staining with benzidine, and the identity of positive band(s) was confirmed by immune electrophoresis.

Results indicate that profound hypotension was accompanied by evidence of diminished tissue perfusion suggested by a significantly increased percentage of iron-laden histiocytes in tracheobronchial secretions (26.0 ± 4.5%) and by the presence of haptoglobin hemoglobin in the electrophoretic strips of five of 10 patients. Moderate hypotension was unassociated with changes in histiocytes or electrophoretic pattern regardless of the technique used to produce the hypotension.

**Key Words:** ANESTHETIC TECHNIQUES: hypotension, induced; BLOOD: hemoglobin degradation.

---

HISTIOCYTES in the tracheobronchial secretions of patients in hemorrhagic shock contain granules which are stained by Prussian blue indicating the presence of intracellular inorganic iron.[1] The serum of these patients may contain one or more of the following products of red cell degradation: (1) haptoglobin-hemoglobin, (2) hemopexin-heme, or (3) methemalbumin. All three may be identified by elec-

---

* Assistant Professor.
† Professor.
‡ Research Fellow.
§ Clinical Assistant Professor.
|| Professor and Chairman.

Received from the Department of Anesthesiology, New York University Medical Center, 550 First Avenue, New York, New York 10016. Accepted for publication November 12, 1979. Presented at the Annual Meeting of the International Anesthesia Research Society, March 11-15, 1979, Hollywood, Florida.

Reprint requests to Dr. Chalon, MD, 9 Tarryhill Rd, Tarrytown, NY 10591.

trophoresis using special staining techniques (amido black and benzidine) and specific immune sera.

Previous work[2] has suggested that the percentage of iron-laden histiocytes in tracheobronchial secretions and the presence of hemoglobin and hemes in serum electrophoresis may provide an index of tissue hypoperfusion. Our concern that profound hypotension during anesthesia may be accompanied by significant impairment of tissue blood flow has led us to apply these techniques in an investigation of patients undergoing intentional controlled hypotension during surgery.

**TABLE 1**

**Techniques Used to Induce Hypotension**

| Technique | No. of patients |
|---|---|
| Profound hypotension with halothane and IPPB* ($\overline{BP}$ 50 torr or below) | 10 |
| Moderate hypotension with halothane and IPPB ($\overline{BP}$ 60–65 torr) | 6 |
| Moderate hypotension with sodium nitroprusside and: | |
| 1. Halothane | 6 |
| 2. Nitrous oxide-narcotic technique | 6 |
| Moderate hypotension with trimethaphan and: | |
| 1. Halothane-nitrous oxide | 6 |
| 2. Nitrous oxide-narcotic technique | 9 |

* IPPB, Intermittent positive pressure breathing.

## Patients and Methods

Forty-three adult patients who had given informed consent were divided into four groups according to the technique used to lower the blood pressure (Table 1). Halothane and intermittent positive pressure breathing were used to induce profound hypotension (mean arterial blood pressure ($\overline{BP}$) 50 torr or below) in 10 patients, and moderate hypotension ($\overline{BP}$ 60 to 65 torr) in six patients. In addition, moderate hypotension was induced using either sodium nitroprusside (12 patients) or trimethaphan camsylate (15 patients), both hypotensive agents being used with either halothane and nitrous oxide or with nitrous oxide and narcotics. Tracheobronchial secretions were collected immediately after induction of anesthesia by suction through the endotracheal tube and again 30 to 60 minutes after the restoration of normotension. Microscope slides of smears were spray-fixed, stained

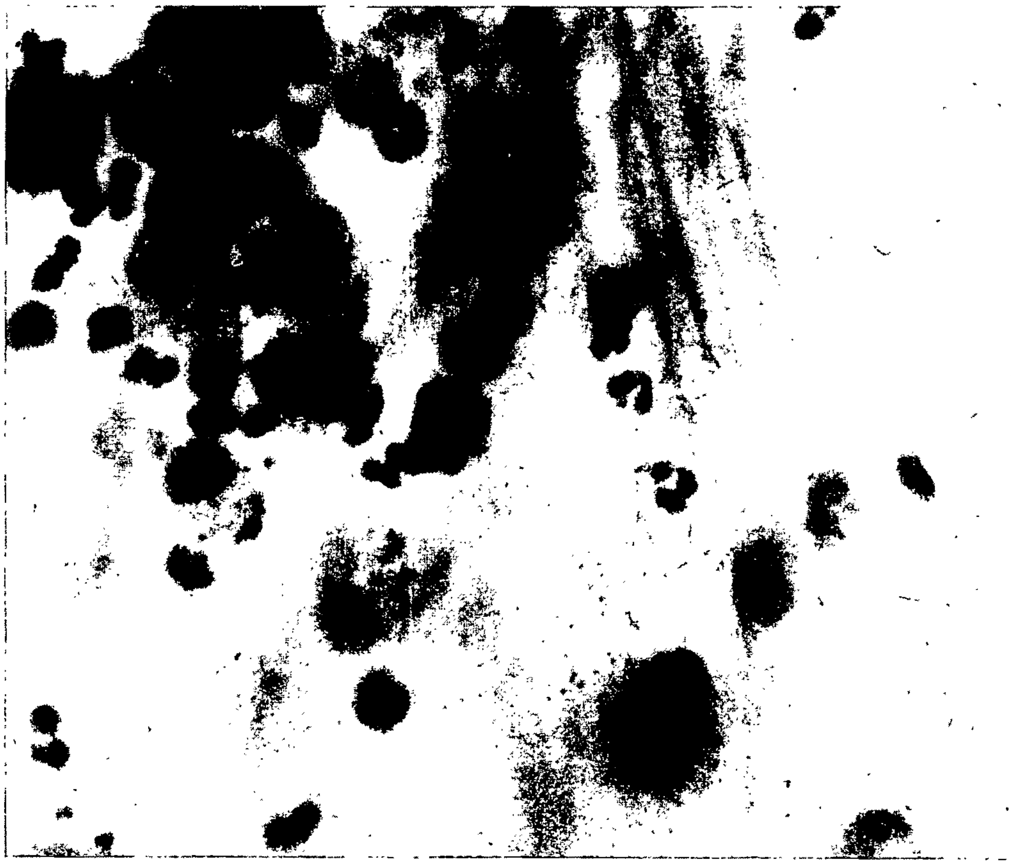


FIG 1. Iron-laden histiocytes (Prussian blue, ×400).

(Prussian blue technique), and examined microscopically (Fig 1). The percentage of histiocytes containing Prussian blue granules (PHFe) in a count of 400 cells was calculated. Immediately after each tracheobronchial suction, 5 ml of venous blood was collected, the serum separated by double centrifugation, and electrophoresis performed using the microlid system of Chuba.[3]

Three electrophoretic strips were run simultaneously, in parallel, on each plate to achieve 2.0- to 2.5-cm separation of proteins. Two of the strips were removed; one was stained with amido black as a reference strip, and the second with benzidine to demonstrate hemoglobin and heme pigments carried on serum proteins. The third strip was used for right-angled immunodiffusion by placing rabbit antisera specific for human haptoglobin and hemopexin in troughs cut parallel to the protein strip. After diffusion the nonreactive proteins were removed by immersion in normal saline. The remaining antigen-antibody reactions were stained with amido black. Three strips were mounted side by side to allow identification of the bands containing organic iron (Fig 2).

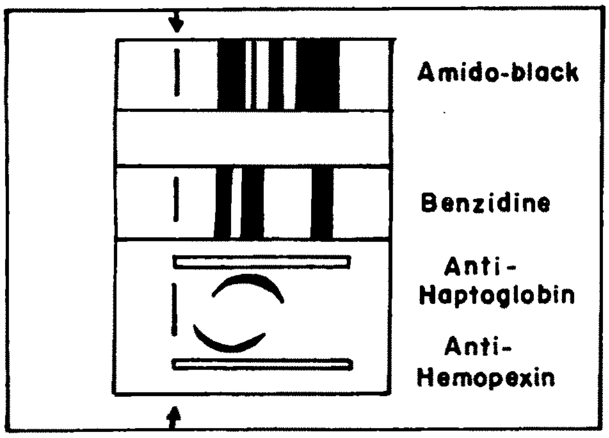


FIG 2. Diagram of the electrophoretic pattern of serum from a patient who died in hemorrhagic shock. Serum methemalbumin band stained by benzidine in line with large albumin band (upper strip). Haptoglobin-hemoglobin and hemopexin-heme bands stained by benzidine in line with anti-haptoglobin and anti-hemopexin precipitate bands (lower strip). No band is found in the middle strip of the serum from normal patients. (Reprinted from the New York State Journal of Medicine (77: 2218, 1977) with permission of the Medical Society of the State of New York.)

Patients were excluded from the study if: (1) blood transfusion was necessary because hypotension failed to prevent bleeding or if minor mismatches caused hemolysis; (2) there was greater than 2 C drop in body temperature; (3) the gel diffusion and benzidine-stained electrophoretic strips showed the presence of haptoglobin-hemoglobin in the first specimen; and (4) the first smear contained more than 2% iron-laden histiocytes. Statistical significance was assessed by currently used variance techniques (*t*-test, chi square) at values of $p < 0.05$.

## Results

The results (Table 2) show a significant increase in the mean PHFe in patients in whom profound hypotension (BP 50 torr or less) was induced by halothane and intermittent positive pressure breathing (IPPB) as well as the presence of organic linked iron as haptoglobin-hemoglobin in the serum in five of 10 patients

**TABLE 2**

**Hypotension Technique and Percentage of Iron-Laden Histiocytes**

| Technique | Mean duration of hypotension* | No. of patients | PHFe† | p | Electrophoresis‡ | | |
|---|---|---|---|---|---|---|---|
| | | | | | 1 | 2 | 3 |
| | *min* | | % | | | | |
| Controls (from previous study)[4] | Normotensive | 10 | 0.4 ± 0.3 | — | — | — | — |
| Halothane and IPPB ($\overline{BP}$ 50 torr or less) | 101 ± 17 | 10 | 26.0 ± 4.5 | <0.0005 | 5 | 0 | 0 |
| Halothane and IPPB ($\overline{BP}$ 60–65 torr) | 86 ± 18 | 6 | 2.6 ± 1.9 | NS§ | 1 | 0 | 0 |
| Sodium nitroprusside ($\overline{BP}$ 60–65 Torr) | | | | | | | |
| 1. $N_2O$-halothane | 107 ± 17 | 6 | 1.0 ± 2.5 | NS | 1 | 0 | 0 |
| 2. $N_2O$-narcotic | 90 ± 19 | 6 | 0.3 ± 0.5 | NS | 0 | 0 | 0 |
| Trimethaphan ($\overline{BP}$ 60–65 torr) | | | | | | | |
| 1. $N_2O$-halothane | 103 ± 17 | 6 | 1.0 ± 1.5 | NS | 1 | 0 | 0 |
| 2. $N_2O$-narcotic | 102 ± 16 | 9 | 1.3 ± 0.6 | NS | 2 | 0 | 0 |

* Values are means ± SE.

† PHFe, Percentage of iron-laden histiocytes at the termination of hypotension. A PHFe of 2% or above in the first specimen excluded the patient from the study. Values are means ± SE.

‡ Electrophoresis code (2nd specimen): A band in the middle strip of the first specimen excluded the patient from the study. 1, haptoglobin-hemoglobin band; 2, hemopexin-heme band; 3, methemalbumin band.

§ NS, Not significant.

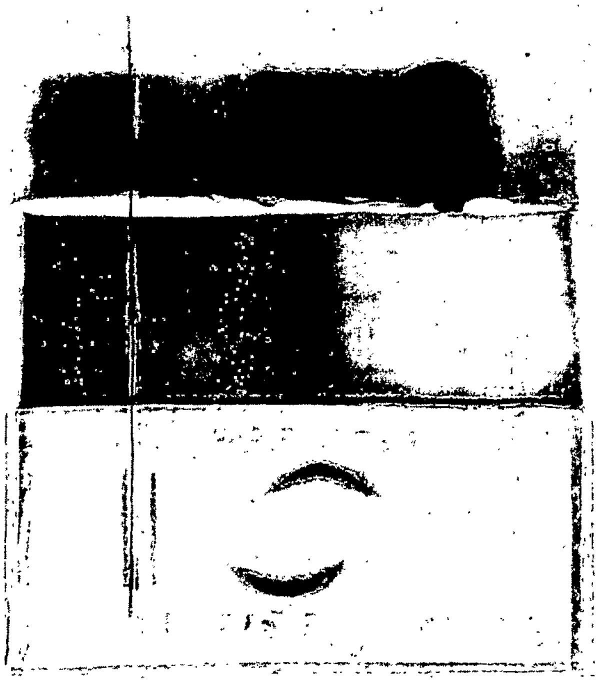


FIG 3. Electrophoretic pattern of a patient undergoing profound induced hypotension with halothane and positive pressure. Note the benzidine-stained band in the haptoglobin (top) and hemoglobin immune interaction areas (bottom).

(Fig 3). There was no significant increase in iron-containing histiocytes or change in electrophoretic pattern in any of the patients subjected to moderate hypotension compared to a control group of 10 normotensive patients reported in a previous study.[4] The mean period of hypotension did not differ significantly in the six groups.

## Discussion

In contemporary clinical practice the use of controlled hypotension is widespread. The advantages to both the surgeon and the patient are well documented,[5-8] but a certain amount of controversy still exists over the means by which the pressure should be lowered.[9-11] Common techniques include the use of halothane and intermittent positive pressure breathing (IPPB), ganglionic blocking agents, and directly acting vasodilator drugs. The mistaken early concept that halothane possesses a ganglionic blocking action and causes little change in cardiac output led to its widespread use as the sole means of reducing the pressure.[12-14] The majority of recent studies suggest a two-phase action of halothane. Initial pressure reduction is due to a decrease in cardiac output resulting from a dose-related depression of myocardial contractility, but with no change in total peripheral resistance. After several hours of anesthesia, however, there is a steady return of cardiac output to or slightly above control levels, with simultaneous reduction of total peripheral resistance.[9, 15, 16] Despite myocardial depression, reduction of myocardial and cerebral oxygen requirement occurs with halothane which may be beneficial in terms of the ratio between oxygen utilization and oxygen supply.[17-20] Notwithstanding, many authors are reluctant to recommend the use of halothane and IPPB alone, but rather advocate the use of halothane and IPPB in conjunction with a ganglionic blocking agent or with a directly acting vasodilator. At present, insufficient data are available to judge the effect of halothane on the oxygen requirement of all body tissues when controlled hypotension is effected in this manner.

Significant impairment of tissue perfusion is accompanied by anaerobic metabolism, lysosomal damage, and release of lysosomal and microsomal enzymes which appear to be proportional to the duration and intensity of the impairment of tissue perfusion.[21] There is evidence that changes in red cell glycolytic activity may cause erythrocytes to rupture (Fig 4). The catabolism of hemoglobin after its appearance in the serum is independent of the mechanism of its release.

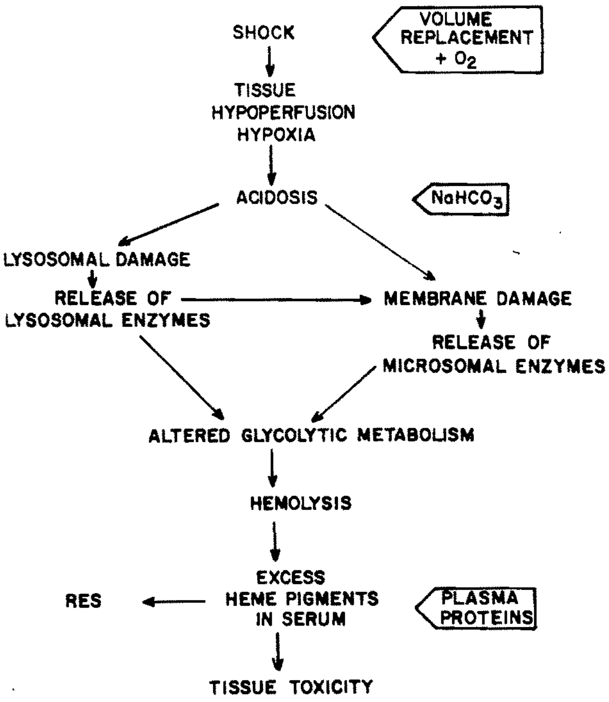

SHOCK
VOLUME REPLACEMENT + O2
TISSUE HYPOPERFUSION HYPOXIA
ACIDOSIS
NaHCO3
LYSOSOMAL DAMAGE
RELEASE OF LYSOSOMAL ENZYMES
MEMBRANE DAMAGE
RELEASE OF MICROSOMAL ENZYMES
ALTERED GLYCOLYTIC METABOLISM
HEMOLYSIS
RES
EXCESS HEME PIGMENTS IN SERUM
PLASMA PROTEINS
TISSUE TOXICITY

FIG 4. Sequence leading to hemolysis in shock and during induced hypotension. (Reprinted from the New York State Journal of Medicine (77: 2218, 1977) with permission of the Medical Society of the State of New York.)

Some of the free serum hemoglobin attaches to haptoglobin (an alpha-globulin) to form haptoglobin-hemoglobin, which is carried to the reticuloendothelial system (RES) (Fig 5). In the RES the hemoglobin is degraded to recycle the iron. If haptoglobin becomes saturated, degradation of free hemoglobin occurs in the presence of acidosis to form toxic heme pigments. Heme is carried in the serum as either free heme, on hemopexin as hemopexin-heme, or on albumin as methemalbumin. Hemopexin (a beta-globulin) has a high affinity for heme but is present in small amounts and thus is quickly saturated. Albumin has a lower affinity for heme but provides a large nonspecific pool available for binding of heme which can only be discharged when free hemopexin reappears.[21] The technique of immunoelectrophoresis allows detection of hemopexin-heme at a concentration of 10 μg/ml and methemalbumin at a concentration of 20 μg/ml. In our patients haptoglobin-hemoglobin was mainly found in the serum of patients undergoing profound hypotension with halothane and IPPB (Fig. 3). The lungs are known to act as a filter for white cells, histiocytes (macrophages and monocytes), and other particles such as fat, amniotic fluid, etc. The increase in the percentage of iron-laden histiocytes in the tracheobronchial secrections, in the presence of hemolysis, indicates effective activity of the RES in the "scavenging" of hemoglobin and its metabolites. A previous study[4] has shown that tracheobronchial secretions normally contain less than 2% iron-laden histiocytes.

Our results show that during profound hypotension induced with halothane and IPPB an abnormal quantity of inorganic iron appears in tracheobronchial histiocytes, a finding which suggests impaired tissue perfusion. However, during moderate hypotension produced by any of the techniques described, there was little or no evidence of excessive free hemoglobin either in the histiocytes of tracheobronchial secretions or in the serum. When halothane is used, the lack of evidence of hemolysis with moderate hypotension makes a drug-related cause unlikely. Of particular interest, the increase in the number of histiocytes found in patients in whom profound hypotension was used correlates well with the presence of haptoglobin-hemoglobin and a high PHFe in reversible shock.[2,4] We suggest that in profound hypotension the right-hand pathway (Fig 5, arrow) is activated, but the degree of acidosis present is insufficient to catabolize the hemoglobin into heme pigments (left-hand pathway). The detection of haptoglobin-hemoglobin in the serum, together with a significant increase in the percentage of iron-containing histiocytes in the tracheobronchial secretions, suggests a degree of impairment of tissue perfusion comparable to that found in mild hemorrhagic shock. However, when moderate hypotension was employed there was no evidence of impaired tissue perfusion with any of the techniques used. All of our patients made an uneventful recovery, irrespective of the method of hypotension used, presumably partly because of the absence of free hemes in their serum which is allegedly toxic to the kidney.[22-24]

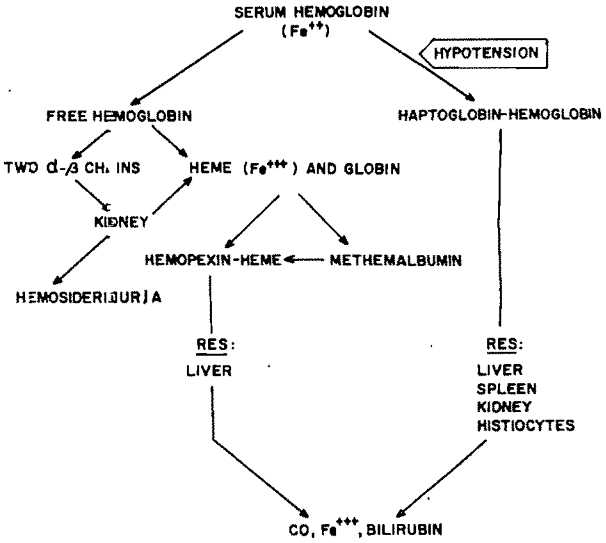


FIG 5. Pathways for catabolism of hemoglobin in shock (both sides) and severe induced hypotension (right only—see arrow). (Reprinted from the New York State Journal of Medicine (77: 2218, 1977) with permission of the Medical Society of the State of New York.)

## REFERENCES

1. Bancroft JD, Stevens A: Theory and Practice of Histological Techniques. New York, Churchill Livingstone Co, 1977, pp 201-202
2. Friedman-Mor Z, Chalon J, Turndorf H, et al: Hemorrhagic shock: concept of toxic elements. NY State J Med 77:2217-2219, 1977
3. Chuba JV: Microimmunoelectrophoresis with improved resolution. Appl Biochem 1:37-50, 1979
4. Friedman-Mor Z, Chalon J, Katz JS, et al: Tracheobronchial and pulmonary cytologic changes in shock. J Trauma 16:58-62, 1976
5. Edwards MW Jr, Flemming DC: Deliberate hypotension. Surg Clin North Am 55:947-957, 1975
6. Schaberg SJ, Kelly JF, Terry BC, et al: Blood loss and hypotensive anesthesia in oral-facial surgery. J Oral Surg 34:147-156, 1976
7. Thompson GE, Miller RD, Stevens WC, et al: Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function. Anesthesiology 48:91-96, 1978
8. Yashon D, Magnes AP II, Vise WM: Systemic hypotension in neurosurgery. J Neurosurg 43:579-589, 1975
9. Adams AP: Techniques of vascular control for deliberate hypotension during anaesthesia. Br J Anaesth 47:777-792, 1975

10. Deutsch S, Linde HW, Dripps RD, et al: Circulatory and respiratory actions of halothane in normal man. Anesthesiology 23:631-638, 1962
11. Prys-Roberts C, Lloyd JW, Fisher A, et al: Deliberate profound hypotension induced with halothane: studies of haemodynamics and pulmonary gas exchange. Br J Anaesth 46:105-116, 1974
12. Raventos J: Action of Fluothane—new volatile anaesthetic. Br J Pharmacol 11:394-410, 1956
13. Johnstone M: Human cardiovascular response to Fluothane anaesthesia. Br J Anaesth 28:392-410, 1956
14. Weaver PC: A study of the cardiovascular effects of halothane. Ann R Coll Surg Engl 49:114-123, 1971
15. Eger EI II, Ty-Smith N, Stoelting RK, et al: Cardiovascular effects of halothane in man. Anesthesiology 32:396-409, 1970
16. Morrow DH, Morrow AG: Effects of halothane on myocardial contractile force and vascular resistance during cardiopulmonary bypass. Anesthesiology 22:537-541, 1961
17. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287-293, 1976
18. Hamilton WK: Do let the blood pressure drop and do use myocardial depressants. Anesthesiology 45:273-274, 1976
19. Michenfelder JD, Theye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trometaphan, halothane or nitroprusside. Anesthesiology 46:188-195, 1977
20. Severinghaus JW, Cullen SC: Depression of myocardium and body oxygen consumption with Fluothane. Anesthesiology 19: 165-177, 1958
21. Muller-Eberhard U: Hemopexin. N Engl J Med 283:1090-1094, 1970
22. Bunn HF, Jandl JH: The renal handling of hemoglobin. II. Catabolism. J Exp Med 129:925-934, 1969
23. Lillehei RC: Relationship of appearance of abnormal plasma hemin pigments to development of irreversible shock in dogs. Circ Res 6:438-441, 1958
24. Pimstone NR, Engel P, Tenhunen R, et al: Inducible heme oxygenase in kidney: a model for the homeostatic control of hemoglobin catabolism. J Clin Invest 50:2042-2050, 1971

---

## Outcome of Surgery and Anesthesia

The outcome of surgery in 500 patients over 80 years of age was studied. Hospital mortality rate within 1 month of surgery was 6.2%. The American Society of Anesthesiologists class 1 to 5 preoperative evaluation scale was useful in predicting death—less than 1% of class 2 patients died, 4% of class 3, and 25% of class 4. Six of seven perioperative deaths were caused by mesenteric infarction. Myocardial infarction was the leading cause of postoperative death. Of 141 patients who underwent upper abdominal surgery 24% required controlled ventilation for more than 24 hours postoperatively, 57% after intrathoracic surgery, and only 2% after surgery that did not enter pleura or peritoneum. No deaths occurred in 47 patients after gallbladder surgery or in 27 patients after peripheral vascular surgery. *(Djokovic JL, Hedley-Whyte J: Prediction of outcome of surgery and anesthesia in patients over 80. JAMA 242:2301-2306, 1979)*

ANESTH ANALG
59:203-206, 1980

# Blood Pressure, Not Cardiac Output, Determines Blood Loss during Induced Hypotension

**Murali Sivarajan, MD* David W. Amory, MD, PhD,† Gaither B. Everett, DDS,‡ and Charles Buffington, MD***

---

SIVARAJAN, M., AMORY, D. W., EVERETT, G. B., AND BUFFINGTON, C.: Blood pressure, not cardiac output, determines blood loss during induced hypotension. Anesth Analg 59:203–206, 1980.

Cardiac output characteristically decreases during trimethaphan infusion but is well maintained or increased during sodium nitroprusside infusion. We postulated that at similar levels of mean arterial pressure, sodium nitroprusside might be associated with greater blood loss than trimethaphan due to the increase in cardiac output. We studied 20 young healthy patients scheduled for bilateral sagittal osteotomies of the mandible. Ten subjects received trimethaphan and 10 subjects received sodium nitroprusside. Using halothane (0.8% to 1%) and nitrous oxide (60%) for maintenance of anesthesia, trimethaphan or sodium nitroprusside was infused to maintain mean arterial pressure between 55 to 60 torr. Cardiac output was measured in five subjects in each group. Heart rate and cardiac output increased significantly and total peripheral resistance decreased significantly during sodium nitroprusside infusion when compared to trimethaphan infusion. There were no significant differences in duration of hypotension or in blood loss. We conclude that operative blood loss during induced hypotension is determined by mean arterial pressure, not cardiac output.

**Key Words:** ANESTHETIC TECHNIQUES: Hypotension, induced.

---

STUDIES in human subjects have shown that cardiac output is significantly decreased during trimethaphan infusion[1, 2] but is well maintained or increased during sodium nitroprusside infusion.[3, 4] Didier et al[1] have suggested that subjective estimation of the dryness of the surgical field correlated better with cardiac output than mean arterial pressure, the field appearing drier and more satisfactory when cardiac output was decreased. We postulated that at similar levels of mean arterial pressure, sodium nitroprusside might therefore be associated with greater blood loss during surgery than would be present if trimethaphan were used, due to an increase in tissue blood flow as a result of the increase in cardiac output associated with nitroprusside. To test this postulate, we measured hemodynamic changes and blood losses in two groups of patients having the same type of surgery; these patients were randomly assigned to receive trimethaphan or sodium nitroprusside.

## Methods and Materials

The study was approved by the institutional Human Subjects Review Committee. Informed consent was obtained from each subject.

The study included 20 subjects, 10 receiving trimethaphan and 10 receiving sodium nitroprusside. Subjects were randomly assigned to receive one of the drugs by drawing the name of the drug from an envelope. Inasmuch as hypotension was the dependent variable, we excluded from the study those subjects in whom we were unable to decrease mean

---

* Assistant Professor.

† Associate Professor.

‡ Associate Professor. Current address: Department of Anesthesia, University of Cincinnati Medical Center, Cincinnati, OH 45267.

Received from the Department of Anesthesiology, RN-10, University of Washington School of Medicine, Seattle, Washington 98195. Accepted for publication November 14, 1979.

Reprint requests to Dr. Sivarajan.

arterial pressure with the drug assigned. Replacement sampling was carried out by returning the slip of paper bearing the name of the drug to the envelope to be drawn once again at random. These methods were used until 10 patients were assigned to each of the two groups.

Subjects of the study were A.S.A. class I patients, ranging in age from 14 to 38 years, scheduled for bilateral sagittal osteotomies of the mandible for correction of malocclusion. All operations were performed by the same surgeon. All patients were premedicated with pentobarbital, 100 to 150 mg IM; fentanyl, 0.05 to 0.1 mg IM; droperidol, 2.5 to 5 mg IM; and atropine, 0.3 to 0.4 mg IM; approximately 45 minutes before they were brought to the operating room. A 16-gauge catheter was placed percutaneously in a peripheral vein for infusion of lactated Ringer's solution and drug administration. A 20-gauge catheter was placed percutaneously in a radial artery for measurement of blood pressure, blood gas tensions, and cardiac output. A 16-gauge central venous catheter was also placed percutaneously via the basilic vein in five of the subjects in each group for injection of indocyanine green. Both arterial and central venous catheters were attached to Statham (P-23ID) pressure transducers. Anesthesia was induced with thiopental, 3 to 4 mg/kg IV, and the trachea intubated via the nasal route 3 to 5 minutes after pancuronium, 0.1 mg/kg IV. Anesthesia was maintained with halothane 0.8% to 1%, nitrous oxide 60%, and oxygen 40% (calculated from individual and total flows). Ventilation was controlled to maintain $Pa_{CO_2}$ between 35 and 45 torr. Subjects were then placed in 15° head-up position. Arterial pressure transducers were placed at the level of the external auditory meatus. Control hemodynamic measurements were made approximately 15 minutes later. Mean arterial pressure was derived by electronic integration of the instantaneous pressure tracing. Cardiac output was measured in duplicate in five subjects in each group by the dye dilution technique using indocyanine green and a Gilford 420 cardiac output computer system.

The throat was packed with preweighed wet sponges before the beginning of surgery. As described above, by random selection subjects were assigned to receive either trimethaphan or sodium nitroprusside. The drug infused was not revealed to the surgeon. The drug was infused with a McGaw volumetric infusion pump. Drug infusion was begun before mucosal incision and the rate of infusion adjusted to maintain mean arterial pressure between 55 to 60 torr. Bleeding during surgery, which was confined to the cavity of the mouth, was aspirated into a suction container. Irrigating fluid was carefully measured. Approximately 30 minutes after induction of hypotension, hemodynamic measurements were repeated. Drug infusion was terminated approximately 10 minutes before the anticipated end of the operation. Blood loss was carefully measured after taking into account volumes of liquid represented by the wet throat packs and the irrigating fluid. The surgeon was asked to score the condition of the surgical field on a scale of 1 to 10, 1 being "dry and ideal" and 10 being "wet and hopeless."

Hemodynamic changes during each drug infusion were compared with control values for the same group using a Student's *t*-test for paired observations. Within each group, age, body weight, heart rate, mean arterial pressure, and blood loss in the five patients in whom cardiac output were measured were compared to the same parameters in the remaining five patients using a Student's *t*-test for unpaired observations. Hemodynamic values, blood loss, and surgeon's score in the two groups were compared using a Student's *t*-test for unpaired observations. Changes were considered statistically significant when $p < 0.05$.

## Results

Within each group, there were no statistically significant differences in age, body weight, heart rate, mean arterial pressure, and blood loss between the five patients in whom cardiac outputs were measured and the remaining five patients. Hence, values for these common parameters for the 10 patients in each group were combined.

Hemodynamic data are summarized in Table 1. Mean values for mean arterial pressures were 53 ± 5 torr during trimethaphan infusion and 56 ± 3 torr during sodium nitroprusside infusion. When compared to control values for the same group, heart rate was significantly decreased by 9% during trimethaphan infusion but significantly increased by 16% during sodium nitroprusside infusion. Trimethaphan produced a significant 37% decrease in cardiac output whereas sodium nitroprusside produced a significant 27% increase in cardiac output. Since decreases in mean arterial pressure and cardiac output during trimethaphan infusion paralleled each other, total peripheral resistance remained unchanged. Sodium nitroprusside, however, produced a 35% decrease in total peripheral resistance. Changes in heart rate, cardiac output, and total peripheral resistance produced by the two drugs were significantly different when compared to each other.

**TABLE 1**

**Hemodynamic Changes during Trimethaphan and Sodium Nitroprusside Infusion***

| | Trimethaphan | | Nitroprusside | | Significance of difference between trimethaphan and nitroprusside groups | |
|---|---|---|---|---|---|---|
| | Control | 30 min | Control | 30 min | Control | 30 min |
| Heart rate (beats/min) | 98 ± 13 | 89 ± 9† | 108 ± 14 | 125 ± 18‡ | NS‖ | $p < 0.001$ |
| Mean arterial pressure (torr) | 76 ± 10 | 53 ± 5§ | 72 ± 6 | 56 ± 3§ | NS | NS |
| Central venous pressure (torr) | 6 ± 4 | 6 ± 3 | 4 ± 2 | 3 ± 2 | NS | NS |
| Cardiac output (L/min) | 6.4 ± 1.4 | 4.1 ± 0.6† | 6.5 ± 0.7 | 8.3 ± 1.4† | NS | $p < 0.01$ |
| Total peripheral resistance (dynes·sec·cm$^{-5}$) | 835 ± 209 | 786 ± 114 | 819 ± 66 | 529 ± 103† | NS | $p < 0.01$ |

* There were 10 subjects in each group but central venous pressure, cardiac output, and total peripheral resistance were measured in only five subjects in each group. Values are means ± SD.

† $p < 0.05$ when compared to control values for the same group.

‡ $p < 0.01$ when compared to control values for the same group.

§ $p < 0.001$ when compared to control values for the same group.

‖ NS, not significant.

**TABLE 2**

**Other Intraoperative Measurements during Trimethaphan and Sodium Nitroprusside Infusion***

| | Trimethaphan (N = 10) | Nitroprusside (N = 10) |
|---|---|---|
| Duration of hypotension (min) | 78 ± 30 | 78 ± 35 |
| Intravenous fluids (ml) (lactated Ringer's solution) | 1640 ± 486 | 1745 ± 579 |
| Blood loss (ml) | 170 ± 102 | 183 ± 92 |
| Surgeon's score | | |
| [1 = dry, ideal<br>10 = wet, hopeless] | 2.0 ± 0.9 | 2.0 ± 1.3 |

* Values are means ± SD.

There were no significant differences in the duration of hypotension, in total intravenous fluids administered, or in blood loss between the two groups (Table 2). Both drugs produced satisfactory surgical fields as indicated by the surgeon's scores and there was no significant difference in the surgeon's score between the two groups (Table 2).

Mean infusion rates of sodium nitroprusside required to maintain mean arterial pressure between 55 to 60 torr varied from a low of 1.3 μg/kg/min to a high of 15.2 μg/kg/min. However, the total dose of sodium nitroprusside did not exceed 1 mg/kg in any of the subjects due to the relatively short duration of hypotension and surgery.

## Discussion

Principal advantages of deliberately induced hypotension are creation of a satisfactory surgical field to facilitate surgery and reduction of blood loss to decrease the need for blood transfusions.[5-7] Although they did not measure blood loss, Didier et al[1] using trimethaphan to induce hypotension, reported that satisfactory surgical field resulted only when decreases in cardiac output were greater than 20%. In four of their 20 subjects who exhibited only small decreases in cardiac output, the surgical field was judged to be unsatisfactory even though there was substantial reduction in mean arterial pressure. But, Amaranath et al,[6] in a retrospective survey, found good correlation (r = 0.84) between systolic blood pressure and estimated blood loss. Thompson et al[7] reported no significant differences in blood loss whether deliberate hypotension was induced with deep halothane anesthesia (2% to 4%), or light halothane anesthesia (0.5% to 1.5%) combined with sodium nitroprusside administration, but they did not measure cardiac output in their subjects.

Hemodynamic changes that we observed with the two drugs are in agreement with previous reports.[1-3] Our findings suggest that bleeding is proportional to mean arterial pressure and not cardiac output. Although sodium nitroprusside produced significant and substantial increases in cardiac output when compared to trimethaphan, blood loss and the condition of the surgical field as reflected by the surgeon's score were not significantly different from that produced by trimethaphan. A possible explanation is that the 15° head-up tilt might have resulted in pooling of blood in the dependent portions so that blood flow to the somatic structures of the head, such as mandible, was purely pressure dependent.

In conclusion, we observed that sodium nitroprusside produced significant increases in heart rate and cardiac output and a significant decrease in total peripheral resistance whereas hypotension produced by trimethaphan was associated with significant decreases in heart rate and cardiac output without a change in total peripheral resistance. At similar levels of mean arterial pressure, there were no significant differences in blood loss and the condition of the surgical field during surgery whether hypotension was induced with trimethaphan or sodium nitroprusside.

### REFERENCES

1. Didier EP, Clagett OT, Theye RA: Cardiac performance during controlled hypotension. Anesth Analg 44:379–386, 1965
2. Jordon WS, Graves CL, Boyd WA, et al: Cardiovascular effects of three techniques for inducing hypotension during anesthesia. Anesth Analg 50:1059–1068, 1971
3. Wildsmith JAW, Marshall RL, Jenkinson JL, et al: Haemodynamic effect of sodium nitroprusside during nitrous oxide/halothane anaesthesia. Br J Anaesth 45:71–74, 1973
4. Styles M, Coleman AJ, Leary WP: Some hemodynamic effects of sodium nitroprusside. Anesthesiology 38:173–176, 1973
5. Eckenhoff JE, Rich JC: Clinical experiences with deliberate hypotension. Anesth Analg 45:21–28, 1966
6. Amaranath L, Cascorbi HF, Singh-Amaranath AV, et al: Relation of anesthesia to total hip replacement and control of operative blood loss. Anesth Analg 54:641–648, 1975
7. Thompson GE, Miller RD, Stevens WC, et al: Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver and kidney). Anesthesiology 48:91–96, 1978

---

## Rebound Phenomenon after Nitroprusside Withdrawal

The hemodynamic events that followed abrupt cessation of nitroprusside infusions were studied in 20 patients with severe chronic heart failure. Nitroprusside increased cardiac index from 1.96 to 2.87 L/min/m$^2$ of body surface area, but after cessation of nitroprusside cardiac index decreased to 1.66 ($p < 0.001$). Left ventricular filling pressure and systemic vascular resistance decreased from 23.9 to 15.3 mm Hg and from 1642 to 921 dyn·sec·cm$^{-5}$, respectively, with nitroprusside, but increased to 30.4 mm Hg and 2109 dyn·sec·cm$^{-5}$ (both $p < 0.001$) upon its discontinuation. These rebound changes were maximal 10 to 30 minutes after nitroprusside withdrawal and returned to control levels 1 to 3 hours later. These rebound changes caused little or no exacerbation of symptoms in 17 of 20 patients, but in three patients pulmonary edema, which resolved with readministration of nitroprusside, developed. Activation of reflex vasoconstrictive forces during vasodilator therapy may explain these effects of withdrawal. *(Packer M, Meller J, Medina N, et al: Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. N Engl J Med 301:1193–1197, 1979)*

ANESTH ANALG
59:207-210. 1980

# Changes in Total Lung/Thorax Compliance following Chest Physiotherapy

**C. F. Mackenzie, MB, ChB, FFARCS,[*] B. Shin, MD,[*] F. Hadi, MD,[†] and P. C. Imle, BS[‡]**

MACKENZIE, C. F., SHIN, B., HADI, F., AND IMLE, P. C.: Changes in total Lung/thorax compliance following chest physiotherapy. Anesth Analg 59:207-210, 1980.

To quantitate and obtain objective assessment of the effect of secretion clearance following chest physiotherapy (CPT), total lung/thorax complicance ($C_T$) was calculated immediately before and for 2 hours after one treatment with CPT. Forty-two patients who were mechanically ventilated because of respiratory failure were studied. Therapy averaged 57 minutes and included postural drainage, percussion, vibration, and endotracheal suctioning. The increase in $C_T$ following CPT was statistically significant ($p < 0.01$) and remained so for at least 2 hours after CPT. There was no difference in the degree to which $C_T$ changed in patients with different indications for CPT or in patients ventilated with positive end-expiratory pressure. Largest mean values for $C_T$ were obtained 2 hours following CPT, the duration of our measurement of $C_T$. Chest x-ray identification of affected areas of lung before CPT is nécessary to allow the physiotherapist to produce the $C_T$ changes noted in this study. $C_T$, which can be readily calculated from many recently designed ventilators, may be monitored during CPT to evaluate the efficacy of treatment and to quantitate the effect of secretion clearance following CPT. Duration of CPT should be determined by $C_T$ and auscultation.

**Key Words:** LUNG: physiotherapy; LUNG: compliance.

MANY AUTHORS[1-3] have noted difficulty in obtaining objective measurements of the benefits that occur in patients with lung disease following removal of airway secretions. Respiratory function tests can be helpful,[4-6] but some, such as forced expiratory volume in 1 second (FeV$_1$), may precipitate small airway closure thereby altering the function that they are assessing.[7] Assessment of effectiveness of secretion clearance by volume of sputum production is notoriously unreliable.[2] Few quantitative data are available in the literature on the efficacy of chest physiotherapy (CPT) in the management of acute lung pathology.[3] even though clinical improvement may result. We have previously reported chest x-ray improvement in 32 of 47 or 68% of patients treated with CPT, the outcome being most dramatic in patients with unilobar atelectasis of acute onset.[9] However, both clinical and radiologic changes are subjective. To obtain an objective assessment, and in an attempt to quantitate the changes occurring following CPT, total lung/thorax compliance was studied immediately prior to and for 2 hours following CPT.

## Methods

In all patients ventilation was mechanically controlled (mean tidal volume 11.5 ml/kg) and they were in phase with the ventilator. Patients were sedated with diazepam and/or morphine; no muscle relaxants were used. Total lung/thorax compliance ($C_T$) was

---

[*] Associate Professor, Department of Anesthesiology.

[†] Instructor, Department of Anesthesiology.

[‡] Staff Physical Therapist, Maryland Institute for Emergency Medical Services Systems.

Received from the Maryland Institute for Emergency Medical Services Systems and the Department of Anesthesiology, University of Maryland, 22 S. Greene Street, Baltimore, Maryland 21201. Accepted for publication November 20, 1979.

Reprint requests should be addressed to Dr. Mackenzie.

calculated from the relationship $C_T = \Delta V/PIEP - PEEP$ where PIEP (cm $H_2O$) was the end inspiratory 'plateau' pressure, PEEP (cm$H_2O$) was the end expiratory pressure, and $\Delta V$ was the inspired volume less the compressible volume ($V_{comp}$ = PIEP × 4.5 ml using standard tubing and humidifier).[10] Inspired minute ventilation was measured from the ventilator flow meters and inspired volume calculated by dividing it by respiratory rate. The lack of direct measurement of expired volume is a limitation of this study, but calculated $V_{comp}$ did not differ significantly from direct measurement in other studies.[11] PIEP was the pressure at end inspiration, which is seen as a pause on the airway pressure gauge. This can be read without ventilator adjustment as the pause is an integral part of the Engstrom ventilator sine wave accelerated flow pattern.[12] PIEP closely approximates alveolar pressure during the no flow period and therefore can be used to estimate $C_T$.[11] $C_T$ was measured with the patient in the supine horizontal position before CPT, immediately upon completion of CPT, and at half-hour intervals for 2 hours thereafter. CPT was performed after identification of the affected lobe or segment using daily portable chest x-rays. CPT included postural drainage, percussion, vibration, and endotracheal suctioning as previously described.[9] Duration of treatment averaged 57 (range 30–110) minutes, at which time the chest was clear to auscultation.

Forty-two patients were studied. Mean age was 34.6 years (range 15–81). There were 31 male patients. All had suffered trauma an average of 5.9 days earlier and had been admitted to the Critical Care Recovery Unit of the Maryland Institute for Emergency Medical Services Systems (MIEMSS) in Baltimore. All patients were ventilated by means of a controlled volume ventilator (Engstrom 300) because of respiratory failure. In 30 patients, PEEP of 4 to 18 cm $H_2O$ was used. The indications for chest physiotherapy included clinical and radiologic evidence of atelectasis in 29 patients, contusion in eight, pneumonia in three, and adult respiratory distress syndrome (ARDS) in two patients. Twenty-two patients had unilobar and 20 multilobar lung pathology. Unilobar densities were found most frequently in the left lower lobe (ten cases), in four the right upper lobe was involved, and in three the right lower lobe. Radiologic densities were infrequently found in the left upper lobe (two cases), in the right middle lobe (two cases), and in the lingula (one case). In seven of the 20 patients with multilobar involvement the lung pathology was bilateral. The paired t-test was used to measure statistical significance.

## Results

A statistically significant ($p < 0.01$) increase in $C_T$ occurred immediately, ½, 1, 1½, and 2 hours following therapy compared to the values before CPT (Figure). Of the 42 patients 37 showed an increase in $C_T$. In 30 patients the increase occurred immediately following CPT. In 25 of the 37 patients the increase in $C_T$ was progressive. The highest levels of $C_T$ were obtained 2 hours following CPT.

The increase in $C_T$ was statistically significant ($p < 0.001$) in the 22 patients with unilobar lung pathology as well as in the 20 patients with multilobar pathology ($p < 0.05$). There was, however, no significant difference in changes in $C_T$ related to whether patients had atelectasis, lung contusion, pneumonia, or ARDS. There was also no significant difference in changes in $C_T$ between patients ventilated with or without PEEP or those treated with CPT for less than or for more than 60 minutes.

Five patients showed no increase in $C_T$ following CPT. Two of these patients who were ventilated with PEEP and had atelectasis showed no change throughout the period of study. Two patients, one with pneumonia the other lung contusion, showed a decrease in $C_T$ for up to 1 hour following therapy before $C_T$ returned to the control level. One patient with a severe lung contusion and copious bloody secretions showed a decrease in $C_T$ of 5 ml/cm/$H_2O$.

## Discussion

The mechanism by which CPT affects $C_T$ is unknown, but CPT is known to enhance movement of

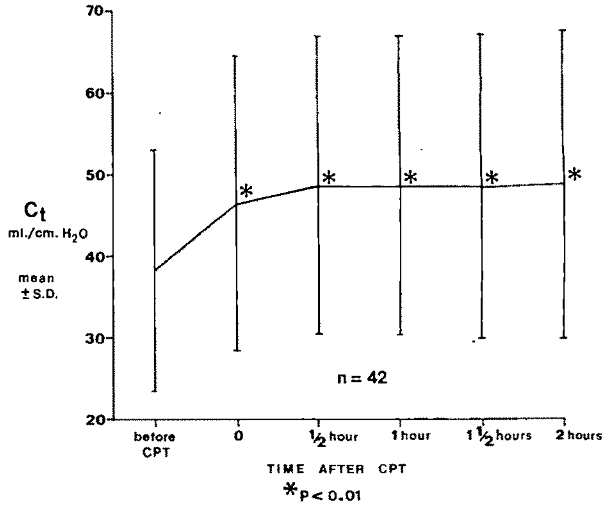


FIGURE. Changes in total/lung thorax compliance in relation to a single treatment with chest physiotherapy.

bronchial secretions from peripheral to more central lung regions and thus to aid in their expectoration[2, 13] and this is thought to be benefical.[2, 3, 8, 14] Alterations in compliance of the lung parenchyma itself are unlikely to be the cause of the rise in $C_T$ that occurred following CPT. Chest wall compliance will influence $C_T$ calculation but since the duration of the study was only a few hours it is unlikely that changes in chest wall compliance sufficent to produce the observed change in $C_T$ would have taken place. Changes in large airways resistance alter peak airway pressure but not end inspiratory pressure and $C_T$ calculation. Therefore, the increase in $C_T$ was probably secondary to the recruitment of more functioning alveolar units as a result of mobilization and clearance of secretions from the small airways. This is also suggested by the finding that increases in functional residual capacity (FRC) following CPT in infants parallel changes in dynamic lung compliance.[15]

The highest mean $C_T$ was obtained 2 hours after CPT, and the rise in $C_T$ was progressive in 25 of the 37 patients. These factors suggest that once secretions have been removed, the airways continue to open up even as long as 2 hours following therapy. Unfortunately, since we did not measure $C_T$ for more than 2 hours after CPT the duration of the observed increase in $C_T$ remains undetermined.

The hypothetical benefits of PEEP in assisting the opening and recruitment of alveoli and the ability to restore FRC[16] have made others suggest PEEP in the management of lobar atelactasis.[17] However, we were unable to show that PEEP made any difference in our patients.

The relatively consistent improvement in $C_T$ following CPT that we report stands in contrast to results reported by others.[3, 4, 6, 18] In part the difference may be due to the fact that in our institution CPT is started within 4 hours of the routine daily portable anteroposterior chest x-ray. This enables the patient to be correctly positioned for postural drainage with the affected lobe or segment as identified by chest x-ray uppermost and thereby allows application of vibration, percussion, and endotracheal suctioning with the patient in the best position to assure drainage.

In some centers CPT on adults lasts only a few minutes,[19] in other centers 7 to 20 minutes,[20] while in some it is restricted to a predetermined duration of 20 minutes.[21] We have found none of these periods sufficient to clear atelectasis in adults or to produce either changes in compliance or radiologic improvement following CPT as we have previously reported.[9] We suggest that therapy should be directed at a specific lobe or segment and should be continued until auscultation reveals signs of improvement such as increased air entry and reduction of adventitial breath sounds. Since the mean treatment time was 57 minutes we suggest that in adults the total time including positioning for postural drainage, percussion, vibration, suctioning, and return to the original position should be about 1 hour. If improvement in $C_T$ and auscultatory signs takes place before this, then therapy can cease. Changes in $C_T$ may be easily observed by the therapist and may be used to evaluate the efficacy of treatment. We could find no associations between changes in $C_T$ and indications for CPT.

Since the inspiratory pause can be made an integral part of the flow pattern of recently designed ventilators such as the MA2, Servo 900, Ohio 560, Forregger 210, and Bear I, this method of calculating $C_T$ should be as easily applied to these ventilators as it is to the Engstrom. Ventilators such as the MAI with "square wave" flow patterns and no expiratory pause can be adjusted to give an approximation to $C_T$ by using the expiratory resistance or inflation hold.[22] However, this maneuver in itself alters the characteristics of the lung being investigated, so that it would be difficult to document changes resulting solely from CPT or other therapies.

In conclusion, measurement of total lung/thorax compliance was clinically useful in quantitation of the effect of secretion clearance following chest physiotherapy in mechanically ventilated patients. The improvement in compliance with chest physiotherapy treatment was significant and lasted for at least 2 hours.

## ACKNOWLEDGMENT

We are grateful to Drs. Chaw and Mahdizadeh who also assisted in this study, and to the other physiotherapists at MIEMSS, Ms. Ciesla, and Ms. Klemic.

## REFERENCES

1. Anthonsen P, Riis P, Søgaard-Andersen T: The value of lung physiotherapy in the treatment of acute exacerbations in chronic bronchitis. Acta Med Scand 175:715–719, 1964
2. Bateman JRM, Newman SP, Daunt KM, et al: Regional lung clearance of excessive bronchial secretions during chest physiotherapy in patients with stable chronic airways obstruction. Lancet I:294–297, 1979
3. Cochrane GM, Webber BA, Clark SW: Effects of sputum on pulmonary function. Br Med J 2:1181–1183, 1977
4. Newton DAG, Stephenson A: Effect of physiotherapy on pulmonary function—a laboratory study. Lancet 2:228–230, 1978
5. Tecklin JS, Holsclaw DS: Evaluation of bronchial drainage in patients with cystic fibrosis. Phys Ther 55:1081–1084, 1975
6. Campbell AH, O'Connell JM, Wilson F: The effect of chest physiotherapy upon the $FeV_1$ in chronic bronchitis. Med J Aust 1:33–35, 1975

7. Nunn JF, Coleman AJ, Sachithanandan, T, et al: Hypoxaemia and atelectasis produced by forced expiration. Br J Anaesth 37: 3–11, 1965
8. Mellins RB: Pulmonary physiotherapy in the pediàtric age group. Am Rev Respir Dis 110 (Part 2):137–142, 1974
9. Mackenzie CF, Shin B, McAslan TC: Chest physiotherapy: the effect on arterial oxygenation. Anesth Analg 57:28–30, 1978
10. Engstrom—Respiratory System ER 300 Instruction Manual VI: 6:8, LKB Medical AB, Stockholm, Arne Tryckare AB, 1974
11. Mackenzie CF, Shin B, Friedman S, et al: Evaluation of total lung/thorax vs static lung compliance. Anesthesiology 51 (Suppl):381, 1979
12. Damman JF, McAslan TC: Optimal flow pattern for mechanical ventilation of the lungs: evaluation with a model lung. Crit Care Med 5:128–136, ;1977
13. Opie LH, Spalding JMK: Chest physiotherapy during intermittent pcsitive pressure respiration. Lancet 2:671–674, 1958
14. Mead J, Collier C: Relation of volume history of lungs to respiratory mechanics in anesthetized dogs. J Appl Physiol 14: 669–678, 1959
15. Fox WW, Schwartz JG, Shaffer TH: Pulmonary physiotherapy in neonates: physiologic changes and respiratory management. J Pediatr 92:977–981, 1978
16. McIntyre RW, Laws AK, Ramanchandran PR: Positive expiratory plateau: improved gas exchange during mechanical ventilation. Can Anaesth Soc J 16:6:477–486, 1969
17. Fowler AA, Scroggins WG, O'Donohue WJ: Positive end-expiratory pressure in the management of lobar atelectasis. Chest 74:497–498, 1978
18. Laws AK, McIntyre RW: Chest physiotherapy: a physiological assessment during intermittent positive pressure ventilation in respiratory failure. Can Anaesth Soc J 16:487–493, 1969
19. Hedstrand U, Liw M, Rooth G, et al: Effect of respiratory physiotherapy on arterial oxygen tension. Acta Anaesthesiol Scand 22:349–352, 1978
20. Gormezano J, Branthwaite MA: Effects of physiotherapy during intermittent positive pressure ventilation. Anaesthesia 27:258–263, 1972
21. Graham WGB, Bradley DA: Efficacy of chest physiotherapy and intermittent Positive pressure breathing in the resolution of pneumonia. N Engl J Med 29:624–627, 1978
22. Bone RC: Compliance and dynamic characteristics curves in acute respiratory failure. Crit Care Med 4:173–179, 1976

---

## Diazepam Prevents Some Adverse Effects of Succinylcholine

Neuromuscular, circulatory, and adverse effects of intravenous succinylcholine (SCh), 1 mg/kg, were compared in three groups of 40 patients each. Group 1 served as control; group 2 received diazepam, 0.05 mg/kg, 5 minutes before SCh; and group 3 was given d-tubocurarine (d-Tc), 0.05 mg/kg, for pretreatment. Diazepam pretreatment prevented muscle fasciculations, increases in serum potassium ($K^+$) and in creatinine phosphokinase (CPK) levels, increases in heart rate and arterial pressure, and postoperative myalgia associated with SCh administration. The neuromuscular blocking action of SCh was not affected. Pretreatment with d-Tc did not abolish increases in serum $K^+$ and CPK levels and was associated with an incidence of postoperative myalgia higher than observed after diazepam; d-Tc also decreased the onset and magnitude of SCh-induced muscle paralysis. Diazepam, a predominant centrally acting muscle relaxant, is more effective than d-Tc in preventing the adverse effects of SCh. *(Fahmy NR, Malek NS, Lappas DG: Diazepam prevents some adverse effects of succinylcholine. Clin Pharmacol Ther 26:395–398, 1979)*

ANESTH ANALG
59:211-214, 1980

# Plasma Cholinesterase Activity in Bank Blood

**Herbert M. Epstein, MD,* Daniel Jarzemsky, BS, Leon Zuckerman, PhD, and Paul Vagher, BS**

---

EPSTEIN, H. M., JARZEMSKY, D., ZUCKERMAN, L., AND VAGHER, P.: Plasma cholinesterase activity in bank blood. Anesth Analg 59:211-214, 1980.

Plasma cholinesterase activity was periodically measured in bank blood. Of the initial plasma cholinesterase activity 87% was retained after 21 days of storage at 4 C in citrate-phosphate-dextrose solution. In addition, plasma frozen for 7 weeks at −70 C showed no decrease in enzyme activity. No difference could be demonstrated in the stability of the enzyme related to whether the blood was stored in citrate-phosphate-dextrose or in acid-citrate-dextrose solution. Bank blood transfusion prior to or during succinylcholine administration should not significantly alter the duration of action of succinylcholine, and would probably be effective in the management of prolonged apnea resulting from a deficiency of this enzyme.

**Key Words:** ENZYMES: plasma cholinesterase; TRANSFUSION: stored blood.

---

SUCCINYLCHOLINE is used in many anesthetic procedures to provide brief periods of muscular relaxation. Its short duration of action is dependent upon rapid enzymatic hydrolysis by plasma cholinesterase (ChE).[1] A 50 to 80% deficiency of this enzyme, such as in liver disease, has been shown to cause a 2- to 3-fold extension of succinylcholine induced apnea.[2] Similarly, genetically atypical variants of this enzyme also result in prolonged responses to succinylcholine.[3,4] Thus, if ChE were not stable in stored blood, massive transfusion could result in a net plasma deficiency and would not be effective in reducing the duration of neuromuscular blockade. The following study was undertaken to determine the ChE activity of stored bank blood preserved with citrate-phosphate-dextrose (CPD) or acid-citrate-dextrose (ACD) solutions.

## Methods and Materials

Fresh whole blood was collected from eight male adults and stored at 4 C in the blood bank. From six of these donors, blood was collected and stored in bags (Fenwal Laboratories, Division of Travenol Laboratories, Inc, Deerfield, IL) containing CPD anticoagulant. Filling volumes were the same in all bags as determined by weight. From each of the two remaining donors, two "half-units" were obtained, one bag containing CPD and another containing ACD as anticoagulant. The volume of anticoagulant solution in these half-units had been adjusted prior to filling to maintain the same dilution as the whole units. These half-units were used to compare the effect on ChE activity of the anticoagulant preservative solution.

Plasma ChE activity was measured periodically in the six whole units and in the four half-units during 21 days of storage. Blood samples were withdrawn from the "leader" of each bag with a sterile needle and syringe using a sterile technique. Prior to sampling, any stagnant blood in the leader was pushed back into the bag, the contents of the bag were mixed gently by hand, and then the blood was allowed to flow back and forth into the leader three times to ensure the collection of a well-mixed sample. After sampling, the leader was heat-sealed immediately

---

* Professor of Clinical Anesthesia, Northwestern University Medical School; Chief, Division of Anesthesiology, Evanston Hospital.

Received from the Department of Research and the Division of Anesthesiology, Evanston Hospital, 2650 Ridge Avenue, Evanston, Illinois 60201 and Department of Anesthesiology, Northwestern University Medical School, Chicago, Illinois. Accepted for publication November 23, 1979.

Reprint requests to Dr. Epstein at Evanston Hospital.

proximal to the puncture site to maintain sterility. Plasma was fractioned by cold centrifugation at 5000 rpm for 10 minutes.

Enzyme activity was measured at pH 7.2 (phosphate buffer) and 25 C by a colorimetric assay (Boehringer Mannheim Corp, #15984). This assay, which is based on a method described by Garry and Routh,[5] employs $5 \times 10^{-3}$ M acetylthiocholine iodide as substrate. Enzymatic hydrolysis of the substrate yields thiocholine and acetate. Liberated sulfhydryl groups then react with 5:5-dithiobis-2-nitrobenzoic acid (DTNB) forming a 5-thio-2-nitrobenzoic acid, a yellow colored derivative.

Optical density was measured every 30 seconds for 3 minutes on a Zeiss PMQ 11 spectrophotometer at 405 nm. Change in optical density per minute was calculated as the slope of a least squares line through the data points. Correlation coefficients ($r^2$) ranged from .9785 to 1.0000, demonstrating that the rate of enzymatic hydrolysis was constant during the assay. Under these conditions enzyme activity is directly proportional to the rate of change in optical density and is expressed as units per milliliter. One unit of enzyme activity is defined as that quantity of enzyme which catalyzes the transformation of 1 μmole of substrate per minute at 25 C.[6]

Cholinesterase activity was also measured in the presence of $10^{-4}$ M dibucaine hydrochloride, a competitive inhibitor of ChE. The degree of inhibition of enzyme activity is expressed in percent as (1 − enzyme activity with inhibition)/uninhibited enzyme activity × 100 and is called a "modified" dibucaine number, since the substrate, substrate concentration, and inhibitor concentration differ slightly from those employed by Kalow and Genest.[7]

Throughout the course of this study all determinations were performed in duplicate. All values in the results section are expressed as means ± standrard error of the mean.

## Results

The serum ChE activity in eight healthy male adults measured immediately prior to donation of blood to be stored was 2.55 ± 0.23 units/ml. Enzyme activity of each donor was within the range of normal values for the assay conditions.[8, 9] Immediately after donated blood had been added to anticoagulant solution plasma ChE activity assayed from samples taken from the blood bag decreased by 17.5 ± 2.0% (CPD) and 21.4 ± 1.2% (ACD). This rapid decrease in enzyme activity at the time of collection can be attributed to dilution of the donor's plasma with the anticoagulant solution in the bag (1:1.25). We simulated the dilution effect by adding proportionate amounts of anticoagulant to prebag samples and found similar decreases in ChE activity: 20.1 ± 0.8% (CPD) and 24.9 ± 0.3% (ACD).

The change in plasma ChE activity in bank blood (CPD) stored at 4 C as a function of time is shown in Fig 1. Data are expressed as a percentage of the initial bank blood enzyme activity. After 21 days of storage the plasma ChE activity was 86.9 ± 1.1% of initial values. A paired *t*-test applied to the data showed this decrease to be statistically significant ($p < 0.001$).

To determine the time course of this decay, plasma ChE activity was measured more frequently in four of the CPD units. Data representing the decay in

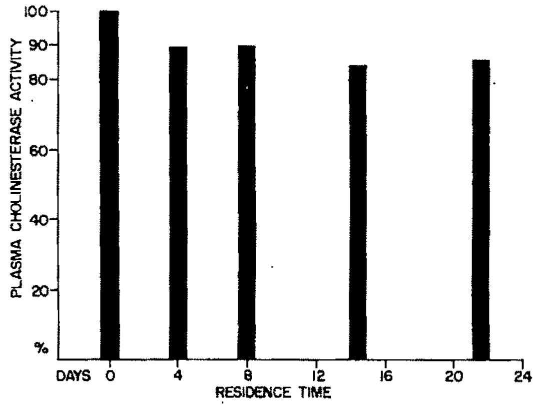


FIG 1. Bar heights represent the plasma cholinesterase (ChE) activity of bank blood stored in citrate-phosphate-dextrose at 4 C. Individual values were normalized as a percentage of their initial determination and then averaged (n = 8). After 21 days of storage 86.9 ± 1.1% of the initial enzyme activity remains ($p < 0.001$).

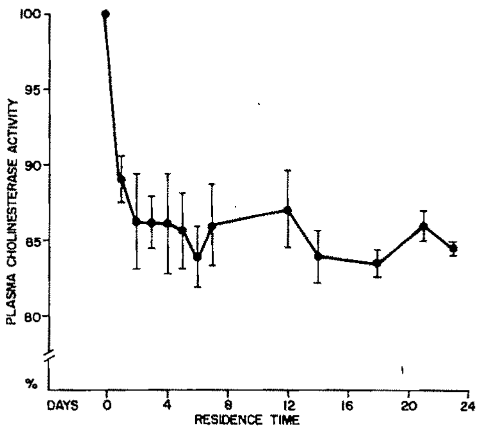


FIG 2. Sequential decay in the plasma cholinesterase activity. As in Fig 1, mean values (n = 4) were calculated from normalized data. Of the total drop in enzyme activity, 88% occurred during the first 2 days of storage.

enzyme activity in each of the four units and the average decay (Fig 2) were analyzed for linear and exponential decay rates. No significant linear or exponential regression in the data was found ($r^2 \leq 0.4$).

The "modified" dibucaine number in bank blood (CPD) was 88.1 ± 1.0% initially (Fig 3), indicating the presence of normal or "usual" plasma ChE enzyme.[10] After 21 days of storage the modified dibucaine number was 81.4 ± 2.1%, a drop of 7.2 ± 2.5%. Based on the paired *t*-test, this small drop was statistically significant ($p < 0.02$).

The decrease in plasma activity in bank blood stored in CPD was not statistically different from blood stored in ACD solution (Fig 4). The anticoagulant solution has no significant effect on plasma ChE stability in bank blood.

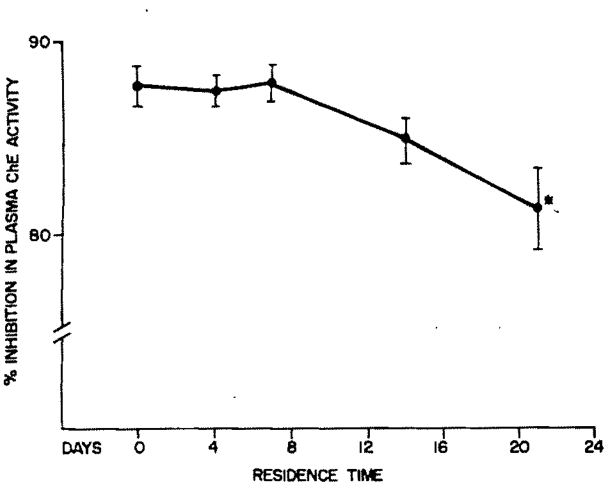


FIG 3. Change in the percent inhibition of plasma cholinesterase activity by $10^{-4}$ M dibucaine. After 21 days the "modified" dibucaine number drops 7.2 ± 2.5% ($p < 0.02$).

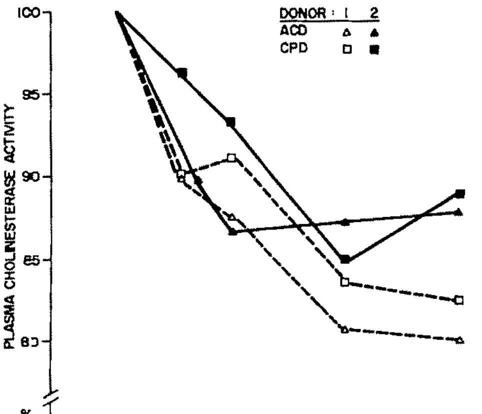


FIG 4. Comparison of plasma cholinesterase stability in two paired units of bank blood stored in acid-citrate-dextrose (ACD) and citrate-phosphate-dextrose (CPD). Variation in the anticoagulant solution has no significant effect on the stability of the enzyme.

## Discussion

Our results indicate that bank blood stored in CPD for 21 days at 4 C retained 87% of the initial plasma ChE activity. While this is at variance with certain previous observations,[11, 12] our data validate the recent studies of both Lanks and Sklar[13] and of Schuh[14] who found no significant change in plasma ChE activity in bank blood stored for 21 days in acid-citrate-dextrose (ACD) anticoagulant solution. Although the 15% fall in enzyme activity is statistically significant, such a decrease would not result in a significant prolongation of apnea using the data of Foldes et al.[2] The decrease estimated from complete replacement by bank blood (87% of normal) would result in a prolongation of apnea from 3.0 to 3.6 minutes from succinylcholine (0.6 mg/kg IV). This change is well within 1 SD of their normal range. In addition, since the modified dibucaine number changed only slightly during storage, it appeared that the qualitative ability of the enzyme to hydrolyze succinylcholine remained unchanged.

Of the total decrease in enzyme activity 88% occurred during the first 2 days of storage. In the remaining 3 weeks, the plasma ChE activity was stable. The cause of this decay was uncertain. Data reported by Callaway et al[15] suggest that this early decline in activity may be linked to the presence of the red cells. If the cells and the plasma were separated and stored at 0 C, plasma ChE activity remained constant for at least 5 days. In our laboratory, plasma frozen at −70 C for 7 weeks showed no loss in ChE activity.

The fate of plasma ChE in vivo reflects the level of potential risk of administration of succinylcholine to patients who have received massive transfusion prior to surgery. Garry et al[16] measured ChE activity following transfusion of 2000 ml of whole blood in a patient identified as being homozygous "silent" for ChE. The half-life of transfused enzyme was found to be 3.4 days. This information, coupled with our findings on the stability of ChE in bank blood, indicates that it is unnecessary to avoid succinylcholine during procedures requiring massive transfusions.

A purified human ChE preparation (Behringwerke) has recently been used to treat prolonged succinylcholine paralysis. Adequate spontaneous respiration was reestablished in 10 minutes after injection of 90 to 135 mg of this preparation.[4, 17] Forty-five milligrams of the enzyme concentrate has a ChE activity equal to 500 ml of fresh human plasma. Transfusion of equivalent amounts of fresh frozen plasma or bank blood plasma might be as effective in reversing prolonged apnea. This concept is supported by Scholler et al[4] who demonstrated that transfusion of 1000 ml of bank blood prevented prolonged apnea after 60 mg of succinylcholine was administered to a patient who was homozygous for "atypical" ChE. Since purified ChE is not available in the United States, transfusion of stored bank blood represents, as our data show, an alternative in the treatment of prolonged neuromuscular blockade after succinylcholine.

In conclusion, plasma cholinesterase activity is well preserved in bank blood stored in CPD. Fresh frozen plasma is an even better source of the active enzyme. Thus, transfusion prior to or during succinylcholine administration should not increase the risk of prolonged apnea. Similarly, fresh frozen plasma or bank blood could be effective as a treatment for prolonged apnea associated with decreased levels of ChE, but the risk of hepatitis should be weighed against the consequences of sustained ventilatory assistance.

## REFERENCES

1. Foldes FF: Distribution and biotransformation of succinylcholine. Int Anesthesiol Clin 13:101-115, 1975
2. Foldes FF, Rendell-Baker L, Birch JH: Causes and prevention of prolonged apnea with succinylcholine. Anesth Analg 35:609, 1956
3. Bauld HW, Gibson PF, Jebson PJ, et al: Aetiology of prolonged apnoea after suxamethonium. Br J Anaesth 46:273-281, 1974
4. Scholler KL, Goedde HW, Benkmann HG: The use of serum cholinesterase in succinylcholine apnoea. Can Anaesth Soc J 24:396-400, 1977
5. Garry PJ, Routh JI: A micro method for serum cholinesterase. Clin Chem 11:91-96, 1965
6. Commission on Biochemical Nomenclature: Enzyme Nomenclature. Amsterdam, Elsevier, 1973, p 22
7. Kalow W, Genest K: A method for the detection of atypical forms of human serum cholinesterase: determination of dibucaine numbers. Can J Biochem Physiol 35:339-346, 1957
8. Weber H: Rasche und einfache Ultramikromethode zur Bestimmung der Serumcholinesterase. Dtsch Med Wochenscher 91: 1927-1932, 1966
9. Szasz G: Cholinesterase Bestimmung im Serum mit Acetyl- und Butyrlthiocholin als Substrat. Clin Chim Acta 19:191-204, 1968
10. Garry PJ: Serum cholinesterase variants: examination of several differential inhibitors, salts, and buffers used to measure enzyme activity. Clin Chem 17:183-191, 1971
11. Hodges RJH, Harkness J: Suxamethonium sensitivity in health and disease: clinical evaluation of pseudocholinesterase levels. Br Med J 2:18-22, 1954
12. Evans FT, Gray PW, Lehmann M, et al: Effect of pseudocholinesterase level on the action of succinylcholine in man. Br Med J 1:136-141, 1953
13. Lanks KW, Sklar GS: Stability of pseudocholinesterase in stored blood. Anesthesiology 44:428-430, 1976
14. Schuh FT: Pseudocholinesterase activity of human whole blood, bank blood, and blood protein solutions. Anaesthesist 24:103-106, 1975
15. Callaway S, Davies DR, Rutland JP: Blood cholinesterase levels and range of personal variation in a healthy adult population. Br Med J 2:812-816, 1951
16. Garry PJ, Prince LC, Notari RE: Half-life of human serum cholinesterase following blood transfusion. Res Commun Chem Pathol Pharmacol 8:371-380, 1974
17. Stovner J, Stadskliev K: Suxamethonium apnea terminated with commerical serum cholinesterase. Acta Anesthesiol Scand 20: 211-215, 1976

# CLINICAL reports

# Another Complication of Armored Endotracheal Tubes

**Kie-Chul Ohn, MD,* and**
**Wen-hsien Wu, MD, MS†**

Armored endotracheal tubes are frequently used during anesthesia when bending or compression of the tube is likely to occur as in neurosurgery or head and neck and oral surgery. However, complications may be associated with use of these tubes. They include collapse of the tube inside the inflated cuff, obstruction caused by folding of the inner wall around the connector[1, 2] or double layering of the cuff preventing deflation.[3] The layering phenomenon is aggravated by repeated autoclaving.[1] Airway obstruction caused by nitrous oxide infiltration of the tube wall during anesthesia has not been described. The present report depicts this type of complication.

## Case Report

A 57-year-old man with an epidermoid carcinoma of the floor of the mouth was scheduled for tracheostomy, bilateral neck dissection, total glossectomy, and partial mandibulectomy. Past medical history was noncontributory except for alcoholism and mild emphysema. Physical examination revealed that the tongue was fixed to the floor of the mouth but was otherwise unremarkable. Arterial blood pH was 7.46; $Pa_{CO_2}$ and $Pa_{O_2}$ were 37 and 87 torr, respectively. After intravenous thiopental (300 mg) and succinylcholine (80 mg), oral tracheal intubation was performed. Anesthesia was maintained with nitrous oxide ($N_2O$, 3 L/min) in oxygen ($O_2$, 2 L/min) and halothane (0.6%) using a circle system. After a tracheostomy, the orotracheal tube was removed and an armored latex rubber endotracheal tube inserted through the stoma. The armored tube had been examined before use for defects by looking through the lumen with the cuff inflated. Respiration was controlled with an Ohio ventilator set to deliver an exhaled tidal volume ($V_t$) of 0.7 L at a frequency of 10/min. Peak inspiratory airway pressure reached 21 cm $H_2O$ with a calculated ventilator compliance of 0.033 L/cm $H_2O$. Exhaled tidal volume was measured on a Dräger Volumeter. Approximately 1 hour after insertion of the tube, airway pressure reached 42 cm $H_2O$. This was associated with prolonged expiration. A suction catheter was passed through the tube without difficulty. Cuff deflation failed to improve the condition. The anesthesia circuit was examined and no obstruction found. Another armored latex rubber tube was examined carefully and inserted after removal of the first.

Airway pressures returned to basal levels. The removed tube was found to have an intramural air bubble which reduced its internal diameter by two thirds (Fig. 1, A). The bubble, 4.5 cm long (Fig. 1, B), was located 20 to 25 cm away from the tube tip and contained 1.4 ml of gas. Approximately 3 hours after insertion of the second tube, the airway pressure rose gradually to 65 cm $H_2O$ with a $V_t$ of 0.45 L, a ventilator compliance of 0.0155 L/cm $H_2O$ (Fig 2, time 0) and a prolonged expiration at the same ventilator settings. Elimination of $N_2O$ from the gas mixture and use of halothane in $O_2$ (5 L/min) brought the airway pressure down to 24 cm $H_2O$ with a $V_t$ of 0.82 L and ventilator compliance up to 0.034 L/cm $H_2O$ in 20 minutes. At this point (Fig. 2, 1st arrow), adding $N_2O$ (3 L/min) to $O_2$ (2 L/min) reproduced the complication in 55 minutes. Anesthesia was, thereafter (Fig 2, 2nd arrow), maintained uneventfully with halothane in $O_2$ and ventilator compliance returned to 0.034 L/cm $H_2O$. Serial arterial blood gas analyses showed neither hypercapnia nor hypoxia during the 13-hour anesthesia. At the end of surgery, the endotracheal tube was replaced by a tracheostomy tube. The second armored tube was found to have a 3-cm bubble within the wall of the tube, 14.5 to 17.5 cm from the tip, obstructing its lumen by two thirds (Fig 1, C). Another small bubble was found elsewhere in the inner wall (Fig 1, D). The air bubbles in both tubes did not connect with the pilot tube.

---

* Resident, Department of Anesthesiology, New York University Medical Center.

† Chief, Anesthesiology Service, Veterans Administration Medical Center; Associate Professor, Department of Anesthesiology, New York University Medical Center.

Received from the Anesthesiology Service, Veterans Administration Medical Center, 408 First Ave., New York, New York 10010. Accepted for publication September 17, 1979.

Reprint requests to Dr. Wu, 77 New Street, Englewood Cliffs, NJ 07632.

## Discussion

Manufacturing of an armored tube requires repeated dipping of wire or nylon coils in latex rubber. During this process dust particles or air bubbles could become implanted within the wall.[2] These bubbles can expand when exposed to $N_2O$. If inward herniation occurs as a result, airway obstruction ensues. Expansion of an intramural air bubble is accelerated by: (1) increased gas concentration gradient across the wall of the bubble, (2) decreased wall thickness, (3) increased gas permeability and solubility through the wall barrier, (4) low molecular weight of the gas, and (5) increased temperature. In this case, factors 3 to 5 above did not vary. Therefore, only the gas concentration gradient and wall thickness of the bubble which was in direct contact with the anesthetics were factors influencing the speed of expansion of a previously present, though not visible, air bubble in the tube wall. The time required for a given air bubble to reach the maximum size is unpredictable. It varies with the concentrations of $N_2O$ and $O_2$ used during anesthesia and with the bubble wall thickness. Because of this unpredictability one must pay special attention to changes in airway pressure and $V_t$ during anesthesia when $N_2O$ is used. When the rise in inspiratory airway pressure and the obstruction become significant and surgery does not permit changing the tube, exclusion of $N_2O$ from the anesthetic mixture can improve the situation by reducing bubble size.

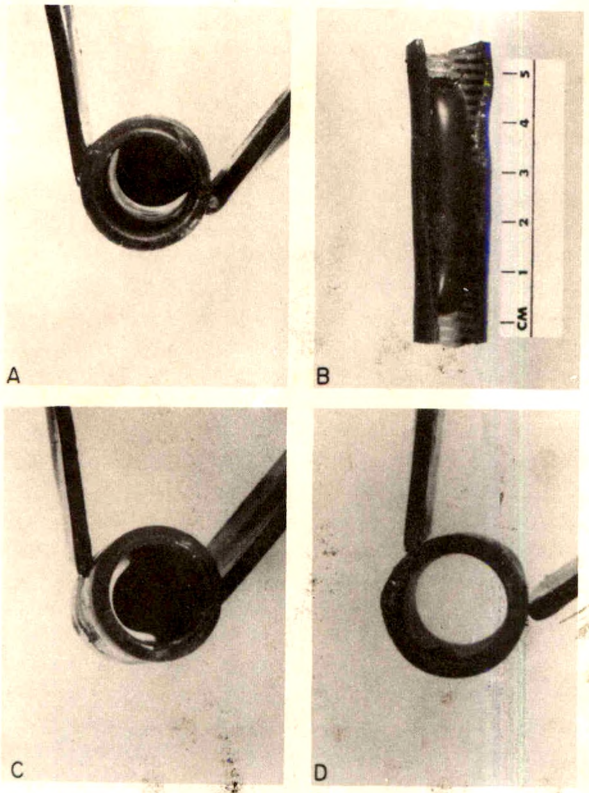


FIG 1. End (A, C) and longitudinal (B) views of two partially obstructed armored endotracheal tubes. A small nonobstructing bubble was seen in the second tube (D).

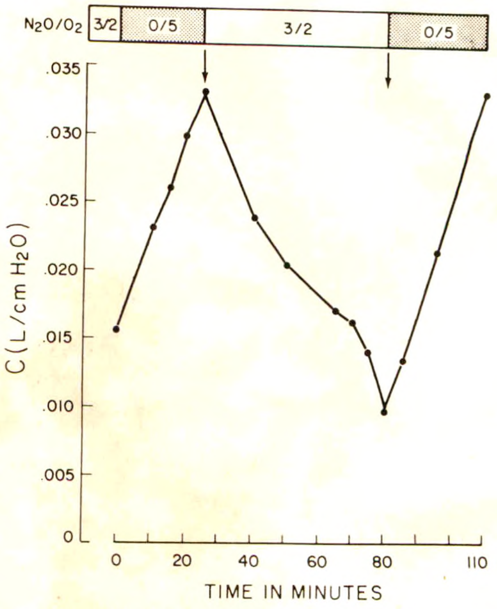


FIG 2. Relationship between inspired $N_2O$ concentrations and ventilator compliance (C) during anesthesia. Fresh gas flows of $N_2O$ and $O_2$ are indicated in liters per minute.

### REFERENCES

1. Jacobson J: A hazard of armored endotracheal anesthesia. Anesth Analg 48:37–41, 1969
2. Robbie DS, Pearce DJ: Some dangers of armored tubes. Anaesthesia 14:379–385, 1959
3. Davis RM: Faulty construction of a reinforced latex endotracheal tube. Br J Anaesth 35:128–130, 1963

ANESTH ANALG
59:217-219, 1980

# Intracardiac Knotting of a Flow-Directed Balloon-Tipped Catheter

**E. E. Fibuch, MD,* and G. F. Tuohy, MD†**

The use of pulmonary artery flow-directed balloon catheters in surgical patients has increased in recent years.[1] Numerous articles[2-5] have documented various complications associated with their insertion and use. The most frequent nonpulmonary complication is the occurrence of cardiac arrhythmias during the catheter insertion.[6] A less frequent but potentially more severe complication is that of internal cardiac knotting.[2] The following report illustrates a case of intracardiac knotting and the possible reasons for its occurrence.

## Case Report

A 76-year-old man was admitted with the preliminary diagnosis of carcinoma of the head of the pancreas. After the appropriate diagnostic work-up, exploratory laparotomy for biliary decompression was performed. During the operative procedure the estimate blood loss was 3000 ml. Postoperatively, the patient continued to bleed from the various abdominal drains; he required 20 units of whole blood and 10 units of platelet concentrate. Due to the continued bleeding, the patient was brought back to the operating room for reexploration of the abdominal cavity.

Prior to induction of anesthesia for the reexploration of the abdominal cavity a pulmonary artery flow-directed balloon-tipped catheter was inserted to aid in monitoring the patient's hemodynamic status and regulating the amount of replacement fluids. After cleaning and draping the left side of the neck a number 18 gauge 4-cm steel needle with an over the shaft Teflon cannula was inserted into the left internal jugular vein without difficulty. (Although the right internal jugular vein is the preferred vein for insertion of a flow-directed pulmonary artery catheter in our institution, it could not be cannulated because of the presence of a previously placed hyperalimentation catheter.) A guide wire was inserted and the Teflon cannula withdrawn. A #8 French dilator with 12.5-cm thin wall external sheath was then inserted over the guide wire into the left internal jugular vein without difficulty. A #7 French thermal dilution pulmonary artery flow-directed catheter attached to a previously calibrated pressure transducer was then inserted rapidly into the right atrium and advanced into the right ventricle while the electrocardiogram and pressure waveforms were monitored oscillographically. After appropriate identification of the right ventricular pressure waveform the balloon of the catheter was inflated with 0.5 ml of air and advanced into the pulmonary artery. Multiple attempts at advancing the catheter from the right ventricle into the pulmonary artery were required before a pulmonary capillary wedge pressure could be measured. The pulmonary capillary wedge pressure was obtained with the catheter inserted 75 cm from the left internal jugular vein. No chest x-ray was obtained at this point.

Approximately 12 hours after the second operative procedure the pressure waveform of the pulmonary artery tracing appeared to be dampened. Flushing the catheter with heparinized saline in an effort to restore a normal pressure waveform was unsuccessful. An attempt to withdraw the catheter and replace it was made; however, after the catheter had been pulled back 30 cm (45 cm still remaining in the patient), resistance to further withdrawal was encountered. At this point an idioventricular rhythm developed and the patient required resuscitation. A chest x-ray was immediately obtained and the tip of the catheter was observed to be in the right pulmonary artery. Although the chest x-ray was nondiagnostic there was some suggestion that the catheter had an abnormal angulation in the right ventricle, appearing to double back upon itself. It was felt that the catheter was either wrapped around a chorda tendineae or was embedded in an organized thrombus in the right ventricle. Attempts at removing the catheter were unsuccessful and in each instance the patient developed multiple focal ventricular premature contractions. Because of the patient's critical condition the catheter was allowed to remain in place. Approximately 48 hours after the second operative procedure the patient died from continued massive bleeding.

At autopsy, the heart, pulmonary artery, and superior vena cava were removed intact. The superior vena cava, right atrium, right ventricle, and pulmonary artery were incised to reveal the course of the pulmonary artery catheter. In the Figure the catheter can be seen passing through the right atrium wrapping and around a chorda tendineae of the tricuspid valve. The catheter is noted to be twisted and knotted in a figure eight configuration before entering the pulmonary artery.

## Discussion

Pulmonary artery flow-directed catheters have been used extensively for monitoring surgical patients.[1]

---

* Staff Anesthesiologist.

† Chairman, Department of Anesthesiology.

Received from the Department of Anesthesiology, St. Luke's Hospital, Kansas City, Missouri 64111. Accepted for publication October 29, 1979.

Reprint requests to Dr. Fibuch.

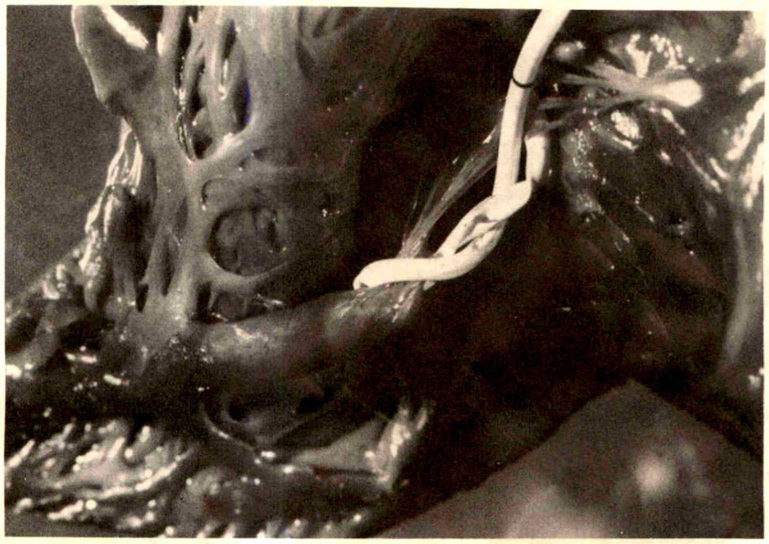


FIGURE. Right atrium and right ventricle have been dissected to reveal the course of the pulmonary artery flow-directed catheter. Catheter can be seen passing through the right atrium (note top of paragraph) and forming a knot around the chorda tendineae of the tricuspid valve. The circumferential black band seen on the catheter at the level of the tricuspid valve is the 50-cm indicator marking. Extensive twisting of the catheter probably occurred during several attempts at its removal.

They have been reported to be easy to insert and generally safe.[1,7] Numerous articles[2-5] have described multiple complications associated with the pulmonary artery flow-directed catheters. The most frequent nonpulmonary complication is development of arrhythmias, generally premature ventricular contractions[6] which tend to occur during passage of the catheter tip through the right ventricle. This is thought to be secondary to mechanical stimulation of the wall of the right ventricle, by the tip of the catheter, particularly when the balloon of the catheter has been deflated.[8] Potentially more serious complications have been reported such as intracardiac knotting[2,5] and perforation of the wall of the right ventricle.[5] Foote et al[5] suggested that the occurrence of intracardiac knotting should never occur when proper catheter insertion technique is used.

After reviewing the technique of catheter insertion in our patient, two facts seem to have contributed to our complication. First, the catheter was advanced 75 cm from the left internal jugular vein before a pulmonary capillary wedge pressure was measured. This is approximately 30 cm longer than is usually required to obtain a pulmonary capillary wedge pressure from the left internal jugular vein. This should have suggested that coiling of the catheter was occurring in the right ventricle. At this point no attempt to withdraw the catheter or to obtain a chest x-ray was made. Second, the balloon was not inflated completely (1.5 ml of air in a #7 French thermal dilution catheter) after it reached the right atrium. Insertion of the catheter with the balloon deflated or with the balloon partially inflated could predispose to migration of the catheter between the wall of the right ventricle and a chorda tendineae or to coiling in the right ventricle.[2,8] The damping of the pulmonary artery pressure waveform in the early postoprative period without improvement following adequate flushing of the catheter with saline should have suggested that kinking or coiling of the catheter had occurred.

This was a serious complication of insertion of a pulmonary artery flow-directed catheter which would have required a major operative procedure for removal.

Although the incidence of intracardiac knotting of flow-directed catheters is unknown, it would appear that serious complications are, in general, rare.[9] The use of proper catheter insertion technique cannot be overemphasized, particularly in reference to inserting the catheter to the recommended distances and keeping the balloon inflated while the tip of the catheter is advanced from the right atrium to the pulmonary artery.

## REFERENCES

1. Civetta JM, Gabel JC: Flow-directed pulmonary artery catheterization in surgical patients. Ann Surg 176:753–756, 1972
2. Lipp H, O'Donoghue K, Resnekov L: Intracardiac knotting of a flow-directed balloon catheter. N Engl J Med 284:220, 1971
3. Chun GMH, Ellestad MH: Perforation of the pulmonary artery by a Swan-Ganz catheter. N Engl J Med 284:1041–1042, 1971
4. Lapin ES, Murray JA: Hemoptysis with flow-directed cardiac catheterization. JAMA 220:1246, 1972
5. Foote GA, Schabel SI, Hodges M: Pulmonary complications of

the flow-directed balloon-tipped catheter. N Engl J Med 290: 927–931, 1974

6. Wennevold A, Christiansen I, Lindeneg O: Complications in 4413 catheterizations of the right side of the heart. Am Heart J 69:173–180, 1965
7. Swan HJC, Ganz W, Forrester JS, et al: Catheterization of the heart in man with the use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447–451, 1970
8. Buchbinder N, Ganz W: Hemodynamic monitoring: invasive techniques. Anesthesiology 45:146–155, 1976
9. Swan HJC, Ganz W: Guidelines for use of balloon-tipped catheter. Am J Cardiol 34:119–120, 1974

---

## Cardiovascular Effects of Pancuronium and Atropine

The ability of pancuronium to increase heart rate, cardiac output, and blood pressure has been attributed to a vagolytic effect, or to a direct or indirect sympathomimetic effect. To investigate the role of the sympathetic nervous system, plasma norepinephrine concentrations were measured following either three doses of pancuronium or one dose of atropine followed by pancuronium in 45 unpremedicated patients anesthetized with halothane and 60% nitrous oxide. Plasma norepinephrine levels and the product of heart rate and systolic blood pressure (rate pressure product) were determined 15 and 18 minutes after stable anesthesia was established. Then either 0, 8, 27, or 80 μg/kg of pancuronium or 5.7 μg/kg of atropine was given intravenously; 3 and 10 minutes later plasma norepinephrine levels and rate pressure product were again determined. In patients not receiving pancuronium or atropine, plasma norepinephrine levels did not change significantly with time. In patients receiving pancuronium alone, plasma norepinephrine levels decreased following pancuronium. The decrease in plasma norepinephrine concentrations following pancuronium correlated significantly with pancuronium dose and was inversely correlated with rate pressure product. The unexpected decrease in plasma norepinephrine levels argues against a sympathomimetic mechanism for the circulatory response to pancuronium. The increase in rate pressure product caused by atropine was also followed by a decrease in plasma norepinephrine levels. Contrasted to the results after pancuronium alone, pancuronium administration after atropine premedication was not followed by a significant increase in rate pressure product or decrease in plasma norepinephrine levels. The authors postulate that the increase in rate pressure product in response to pancuronium (or atropine) acts through baroreceptors to reduce sympathetic outflow. *(Roizen MF, Forbes AR, Miller RD, et al: Similarity between effects of pancuronium and atropine on plasma norepinephrine levels in man. J Pharmacol Exp Ther 211:419–422, 1979)*

## Analysis of Surgical Blood Use

Excessive preoperative cross matching can be limited with a maximum surgical blood order schedule (MSBOS) which is a list of the commonly performed elective surgical procedures performed in a hospital with the maximum number of units of blood which will be cross matched preoperatively for each. The purpose of this study was to analyze the blood requirements of 535,031 surgical patients treated in 300 United States hospitals during 1974, and to suggest maximum preoperative blood orders including type and screen recommendations based on data derived from this large national patient sample. Such recommendations are offered for 63 common elective surgical procedures. Specific reference is made to blood utilization during hysterectomy, transurethral resection of the prostate, and cesarean section. A preoperative type and screen order is adequate for the vast majority of patients undergoing these procedures. The author suggests that major reductions in the volume of blood cross matching for elective surgery can be achieved without adversely affecting patient care. *(Friedman BA: An analysis of surgical blood use in United States hospitals with application to the maximum surgical blood order schedule. Transfusion 19:268–278, 1979)*

ANESTH ANALG
59:220–221, 1980

# Malignant Hyperthermia: A Case Report

**Peter M. Waterman, MD,* Maurice S. Albin, MD,† and R. Brian Smith, MD‡**

Certain drugs such as succinylcholine and halothane are recognized as capable of precipitating malignant hyperpyrexia in susceptible individuals. Other drugs used in anesthesia have also been reported as triggering agents, but their role remains less clearly defined. Pancuronium has not been reported as a triggering agent for malignant hyperpyrexia. We report a case of apparent malignant hyperpyrexia in which pancuronium may have been the triggering agent.

## Case Report

A 25-year-old, 80 kg, white man was admitted for radical periaortic lymph node dissection under general anesthesia. He had undergone uneventful general anesthesia for orchiectomy 1 week previously at another hospital for embryonal carcinoma (teratocarcinoma). Anesthesia at that time consisted of sodium thiopental, nitrous oxide, and halothane. Gallamine (20 mg) and succinylcholine (100 mg) were used for endotracheal intubation. Temperature was not monitored. There was no record of difficulty encountered with this previous anesthetic. Following orchiectomy the patient was transferred to Presbyterian-University Hospital for further evaluation. Liver function tests, serum electrolyte levels, and urinalysis were all within normal limits. The evening prior to surgery he received 1000 μg of actinomycin D as his first dose of chemotherapy.

On the morning of the operation the patient's temperature was 37 C prior to preoperative medication consisting of meperidine (100 mg), promethazine (25 mg), and glycopyrrolate (0.4 mg) intramuscularly 1 hour before the scheduled time of surgery. Skin temperature upon arrival in the operating room was noted to be cool. Anesthesia was induced using intravenous fentanyl (0.2 mg), diazepam (10 mg), and thiamylal sodium (100 mg). Endotracheal intubation was facilitated by pancuronium (8 mg). Five minutes after injection of pancuronium, the patient had a tachycardia of 140 beats per minute. The pulse rate prior to induction had been 80 beats per minute. The elevation of pulse rate was attributed to the light plane of anesthesia and to the pancuronium. The patient had no rigidity, but as the abdomen was prepared prior to draping, his skin felt hot to the touch. A LaBarge Mon-a-therm tympanic temperature sensor with the probe in the right ear registered 39 C. Simultaneously a Yellow Springs Instruments esophageal probe confirmed the 39 C temperature. Anesthesia was immediately discontinued and cooling procedures initiated. The patient was placed on a cooling blanket and iced saline was given via two indwelling 14-gauge catheters. Arterial and central venous catheters were inserted. Droperidol (5 mg), dexamethasone (20 mg), and procaine amide (1 gm) were administered intravenously. Hyperventilation was instituted immediately upon recognition of the temperature elevation. As the anesthesia tubing was new and the anesthesia machine did not contain halothane, there was no need to change to another anesthesia circuit.

Arterial blood obtained in the operating room showed, when subsequently analyzed, laboratory data as follows: serum creatine phosphokinase (CPK) 260 IU, serum aldolase 3.2 mU/ml, serum lactate 4.2 meq/L, and serum $K^+$ 3.2 meq/L. Arterial gases ($F_{IO_2}$ 1.0, respiratory rate 25 breaths per minute, and tidal volume 1000 ml) were pH 7.16, $P_{CO_2}$ 31 torr, $P_{O_2}$ 468 torr, $HCO_3$ 11 meq/L, and base excess −17 meq/L. Two hundred milliequivalents of $NaHCO_3$ was administered. Within 45 minutes the temperature was 37.5 C and cooling was discontinued. An arterial blood sample with the same ventilatory settings showed pH to be 7.61, $P_{CO_2}$ 20 torr, $P_{O_2}$ 455 torr, $HCO_3$ 20 meq/L, and base excess +1 meq/L. The ventilator was readjusted appropriately.

After the temperature decreased, the patient was transported to the intensive care unit where he made an uneventful recovery. Three hours after reaching the recovery area the endotracheal tube was removed. Serum aldolase and lactate levels returned to normal over the next 3 days. Serum CPK levels remained elevated approximately three times above normal on the second and third postoperative days. Three weeks later the serum CPK level had returned to the normal value of 13 IU.

Six weeks later the patient presented again for radical periaortic lymph node dissection. He was pretreated with oral dantrolene sodium (100 mg qid) for 3 days prior to operation. Preoperative medication consisted of Innovar (1 ml IM) 90 minutes prior to his operation. Induction of general anesthesia was accomplished with thiamylal sodium (300 mg) and Innovar (5 ml IV). Endotracheal intubation was accomplished without the use of muscle relaxants. After intubation the patient was turned and a catheter

---

* Assistant Professor, Department of Anesthesiology, University Health Center of Pittsburgh.

† Professor of Anesthesia, Department of Anesthesiology, University of Texas Health Sciences Center at San Antonio.

‡ Professor and Chairman, Department of Anesthesiology, University of Texas Health Sciences Center at San Antonio.

Received from the Department of Anesthesiology, University Health Center of Pittsburgh, Pittsburgh, Pennsylvania 15261. Accepted for publication November 13, 1979.

Reprint requests to Dr. Waterman, Department of Anesthesiology, Presbyterian-University Hospital, DeSoto at O'Hara Sts, Pittsburgh, PA 15213.

inserted into the subarachnoid space. Muscle relaxation was then provided using intermittent injections of tetracaine through the catheter. The operation lasted 11 hours, during which general anesthesia was maintained with $N_2O$ supplemented with fentanyl. Temperature was monitored throughout via nasal, esophageal, and rectal temperature probes. Arterial blood gases obtained via an indwelling radial artery catheter remained within normal limits during the operation and the recovery period. His recovery was uneventful and he was discharged on the tenth postoperative day.

## Discussion

Current theories regarding the cause of the malignant hyperthermia include the concept of unrestricted ionic calcium flow from the sarcoplasmic reticulum into the cytoplasm of skeletal muscle.[1] Dantrolene sodium is felt to be effective in the management of malignant hyperpyrexia by preventing the initial release of calcium. Dantrolene was unavailable when this case occurred. Studies involving the preoperative preparation of patients susceptible to malignant hyperthermia with oral dantrolene[2] as well as studies using intravenous dantrolene in the treatment of a malignant hyperthermia crisis are currently underway.[3(p53)] Therapy with procaine HCl, procaine amide, and haloperidol facilitates re-uptake of calcium back into the sarcoplasmic reticulum, which terminates the event.[1]

Our case is interesting in that it represents an instance in which malignant hyperthermia occurred in conjunction with the use of pancuronium. Cain and Ellis[4] indicate that the steroid base of pancuronium may protect against development of malignant hyperthermia by stabilizing the sarcoplasmic reticular membrane. They suggest[4] that pancuronium may be a "suitable drug for use in patients susceptible to malignant hyperthermia." Britt and others, however, recommend that in the elective management of patients susceptible to malignant hyperthermia, regional techniques utilizing ester-type local anesthetics be employed to provide skeletal muscle relaxation.[3(p66)] Dexamethasone has been reported useful in the treatment of malignant hyperthermia in conjunction with peripheral cooling.[5] The current case was treated with dexamethasone together with droperidol, procaine amide and peripheral cooling.

Pancuronium may not have been the cause of this patient's hyperpyrexia. Promethazine-HCl was used as a preoperative medication. Moyes[6] has reported the death of a 3-year-old boy following the intramuscular injection of another phenothiazine, trimeprazine, as a premedicant. Moyes's patient became ill within 15 minutes of injection and after an 80-hour course of fever, acidosis, and rigidity finally succumbed to pulmonary failure. Ellis et al[5] described a case of malignant hyperthermia in an 11-year-old girl in which nitrous oxide appeared to be the inciting agent. In their case the patient was successfully treated with dexamethasone and later underwent uneventful general anesthesia with thiopental alone. Our patient developed tachycardia and elevation of temperature during induction of anesthesia prior to use of nitrous oxide. Stress may have played a significant role, having acted as a triggering agent in a number of cases as well as in the animal model of porcine hyperthermia.[1,3(p[illegible]3),5,7,8] Wingard[3(p79)] reports 20 human deaths due to malignant hyperthermia, none of which were related to anesthesia. Our patient was anxious, as might be expected under the circumstances. He had recently been told of the diagnosis of carcinoma and fully realized the significance of his staging procedure. There has been no mention in the literature of a relationship between cancer chemotherapy, in this case actinomycin D, and malignant hyperthermia; but one may exist.

The issue of what triggers the malignant hyperthermia crises remains in doubt. In fact, some agents thought to be triggers are now questionable.[9] In this case phenothiazines, muscle relaxants, stress, and anticancer drugs were all present. Perhaps the answer lies somewhere in the perioperative milieu, rather than with one specific agent, but perhaps pancuronium may have been contributory and it is for this reason that we report this case.

### REFERENCES

1. Britt BA: Etiology and pathophysiology of malignant hyperthermia. Fed Proc 38:44–48, 1979
2. Pandit K, Kothany S, Cohen P: Orally administered dantrolene for prophylaxis of malignant hyperthermia. Anesthesiology 50: 156–158, 1979
3. Wenschel EO: Malignant Hyperthermia. New York, Appleton-Century-Crofts, 1977, pp 53, 66, 79
4. Cain PA, Ellis FR: Anaesthesia for patients susceptible to malignant hyperpyrexia. Br J Anaesth 49:941–944, 1977
5. Ellis FR, Clark IMC, Appleyard TN, et al: Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. Br Med J 4:270–271, 1974
6. Moyes DG: Malignant hyperpyrexia caused by trimeprazine. Br J Anaesth 45:1163–1164, 1973
7. Britt BA, Kalow W: Malignant hyperthermia: a statistical review. Can Anaesth Soc J 17:293–315, 1970
8. Mogensen JV, Misfeldt BB, Hanel HK: Preoperative excitement and malignant hyperthermia. Lancet 1:461, 1974
9. Wingard DW, Bobko S: Failure of lidocaine to induce porcine malignant hyperthermia. Anesth Analg 58:99–103, 1979

ANESTH ANALG
59:222–224, 1980

# Avoidance of Heparin Contamination in Coagulation Studies Drawn from Indwelling Lines

**Louis M. Palermo, MD,***
**Raymond W. Andrews, BS,† and**
**Norig Ellison, MD‡**

Use of continuous low dose heparin flush solutions to maintain patency of indwelling arterial lines is a widely accepted practice.[1] Although the primary purpose of these lines is to measure arterial or venous pressure continuously, the lines also provide a readily available portal for obtaining blood samples. However, the possibility of heparin contamination of such samples has prompted some authorities to question obtaining blood samples for coagulation studies from indwelling arterial lines.[2, 3] Table 1 lists values from two patients whose blood samples were deliberately contaminated by inadequate clearing of the deadspace, showing the abnormal studies which can be produced. This study was approved by The University of Pennsylvania Committee on Human Experimentation.

## Methods and Materials

Patients scheduled for open heart surgery who had a normal preoperative coagulogram (activated partial thromboplastin time, prothrombin time, activated coagulation time, and platelet count) were studied.

Deadspace in our line systems is 1.79 cc for the arterial line and 1.50 cc for the central venous pressure (CVP) port of the pulmonary artery catheter. Before connecting the arterial cannula to the heparin flush line, control values were obtained to ensure that there had been no possibility of heparin contamination. After the arterial and CVP lines had been in place for 30 minutes, with heparin flush being infused at a rate of 5 to 7 ml/hour (C.F.S. Intraflo, Sorenson Research Co, Salt Lake City, UT) in each line, and after withdrawing the respective deadspace volume and additional discard volumes equal to 0, 1-, 2-, and 4-ml samples were obtained. The following tests were run in each sample.

### Automated Activated Coagulation Time (ACT)

Three milliliters of blood from each sample was placed in a CA510 Hemochron (International Technidyne, Metuchen, NJ) tube and ACT measured in duplicate.[4]

### Activated Partial Thromboplastin Time (aPTT)

Four and one-half milliliters of blood from each sample was placed into a test tube containing 0.5 ml 0.1 M sodium citrate (final dilution 1:10) and mixed well. A hematocrit was obtained and then the sample was centrifuged to obtain plasma for measuring the aPTT manually.[5]

### Protamine Titration Test

Pairs of test tubes were prepared immediately before sampling: a control tube was left empty and 10 μg of protamine placed in the second tube with a microliter syringe (Repeating dispenser PB-600-1 and microliter syringe 705-N, Hamilton Co, Reno, NV), both tubes being maintained in a constant temperature block at 37 C. One milliliter of blood was added to each tube and an elapsed time indicator started. Each tube was gently tilted 90° every 30 seconds until the tube could be inverted without causing the blood to flow. In samples containing no heparin, the control tube clotted before the tube with protamine.[6]

Two groups of six patients were studied. In one group the heparin flush concentration contained 1 unit of heparin per milliliter of flush solution; in the second group, there were 2 units of heparin per milliliter of flush solution.

## Results

Table 1 illustrates the markedly abnormal values that can be obtained when deliberate contamination with the heparin flush solution was produced, viz,

---

* Fellow, Department of Anesthesia, University of Pennsylvania.

† Research Technician, Department of Anesthesia, University of Pennsylvania.

‡ Associate Professor of Anesthesia, Hospital of the University of Pennsylvania.

Received from the Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104. Accepted for publication November 19, 1979.

Reprint requests to Dr. Ellison.

slight prolongation of ACT, marked prolongation of aPTT, and evidence of heparin effect on the protamine titration.

Table 2 shows the results in the two groups of patients when the deadspace plus additional discard volumes of 0, 1, 2, and 4 ml of blood are withdrawn prior to sampling. In the group in which the heparin flush contained 2 units of heparin per milliliter the aPTT was slightly prolonged in the two samples where the discard volume was equal to the deadspace and to the deadspace plus 1 ml. However, none of the changes was statistically significant. In fact at no time in either group was a significant change from the control value observed for any test as long as a volume equal to the deadspace was first withdrawn. Hematocrits were slightly decreased below control values in all groups, with insignificant variance.

**TABLE 1**

**Comparison of Coagulation Studies in Two Patients When Adequate/Inadequate Aliquots Are Withdrawn Prior to Collecting Sample for Testing***

| Patient | Aliquot (ml) withdrawn prior to collecting sample | ACT | aPTT | Protamine titration | | Hct |
|---|---|---|---|---|---|---|
| | | | | Without protamine | With protamine | |
| | | *sec* | | *min* | | *%* |
| 1 | = deadspace (1.8 ml) | 122 | 43.7 | 3.00 | 3.50 | 28.8 |
| | = ½ deadspace | 129 | 104.5 | 5.00 | 3.25 | 28.0 |
| 2 | = deadspace | 130 | 37.4 | 3.50 | 4.00 | 30.5 |
| | = ½ deadspace | 138 | 57.9 | 4.25 | 3.75 | 24.2 |

* Abbreviations used are: ACT, activated coagulation time; aPTT, activated partial thromboplastin time; Hct, hematocrit.

## Discussion

Critically ill patients may require frequent coagulation studies during critical periods.[6, 7] The advantage of obtaining samples for these studies from indwelling lines is obvious to the anesthesiologist in the operating room where the patient's arms may not be readily available. In patients with a hemorrhagic diathesis, avoidance of venopuncture with possible attendant

**TABLE 2**

**Coagulation Studies in Two Groups of Six Patients Comparing Results When Varying Aliquots of Heparin Flush Solutions and Blood Are Withdrawn Prior to Sampling**

| Heparin flush concentration | | Arterial line (deadspace (DS) = 1.79 ml) | | | | | Venous line (deadspace (DS) = 1.50 ml) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Control | DS + 0 | DS + 1 | DS + 2 | DS + 4 | Control | DS + 0 | DS + 1 | DS + 2 | DS + 4 |
| 1 unit/ml (N = 6) | | | | | | | | | | | |
| ACT | x̄ | 116.8 | 119.2 | 115.3 | 115.1 | 113.6 | 119.1 | 114.1 | 110.6 | 107.9 | 108.6 |
| (sec) | SEM | 4.60 | 3.67 | 3.67 | 4.06 | 4.65 | 4.61 | 2.06 | 1.70 | 2.21 | 3.19 |
| aPTT | x̄ | 43.3 | 48.6 | 43.2 | 42.6 | 41.4 | 44.4 | 47.6 | 43.9 | 43.3 | 43.3 |
| (sec) | SEM | 3.49 | 3.52 | 3.14 | 3.24 | 2.97 | 3.21 | 4.23 | 3.77 | 3.56 | 3.99 |
| Hct | x̄ | 32.2 | 30.2 | 31.1 | 31.5 | 31.4 | 30.0 | 28.5 | 28.2 | 28.2 | 27.7 |
| (%) | SEM | 1.96 | 1.68 | 1.97 | 1.87 | 1.84 | 1.88 | 1.55 | 1.76 | 1.77 | 1.82 |
| Protamine titration (min) | | | | | | | | | | | |
| Without protamine | x̄ | 3.43 | 3.52 | 3.08 | 3.30 | 3.24 | 3.35 | 3.08 | 2.81 | 2.65 | 2.59 |
| | SEM | 0.21 | 0.17 | 0.14 | 0.17 | 0.20 | 0.22 | 0.15 | 0.16 | 0.11 | 0.19 |
| With protamine | x̄ | 4.12 | 3.92 | 3.92 | 3.94 | 4.0[illegible] | 4.06 | 3.67 | 3.41 | 3.23 | 2.98 |
| | SEM | 0.27 | 0.15 | 0.14 | 0.10 | 0.13 | 0.29 | 0.12 | 0.21 | 0.21 | 0.16 |
| 2 units/ml (N = 6) | | | | | | | | | | | |
| ACT | x̄ | 118.0 | 117.3 | 113.4 | 114.2 | 111.1 | 120.3 | 115.8 | 111.7 | 106.6 | 103.3 |
| (sec) | SEM | 1.97 | 2.35 | 1.48 | 2.06 | 1.67 | 2.73 | 1.78 | 2.93 | 7.88 | 3.42 |
| aPTT | x̄ | 40.3 | 44.2 | 43.4 | 41.2 | 41.8 | 38.0 | 40.4 | 39.0 | 38.4 | 36.5 |
| (sec) | SEM | 2.65 | 4.04 | 3.63 | 3.41 | 3.53 | 1.45 | 3.20 | 2.09 | 2.25 | 1.23 |
| Hct | x̄ | 34.3 | 32.1 | 32.8 | 32.5 | 32.4 | 33.6 | 30.6 | 30.9 | 30.9 | 31.0 |
| (%) | SEM | 1.02 | 1.21 | 1.49 | 1.50 | 1.3[illegible] | 1.19 | 1.19 | 1.31 | 1.44 | 1.71 |
| Protamine titration (min) | | | | | | | | | | | |
| Without protamine | x̄ | 3.58 | 3.29 | 3.29 | 3.08 | 3.13 | 3.58 | 3.08 | 3.08 | 2.88 | 2.83 |
| | SEM | 0.20 | 0.10 | 0.10 | 0.14 | 0.13 | 0.20 | 0.08 | 0.11 | 0.09 | 0.11 |
| With protamine | x̄ | 4.08 | 3.83 | 3.83 | 3.67 | 3.7[illegible] | 4.04 | 3.54 | 3.58 | 3.58 | 3.58 |
| | SEM | 0.21 | 0.11 | 0.18 | 0.15 | 0.1[illegible] | 0.21 | 0.12 | 0.11 | 0.15 | 0.08 |

bleeding and oozing is distinctly advantageous. This is especially true in cases where repeated sampling is necessary to run serial tests as the response to therapy is measured. Whereas the possibility of heparin producing prolongation of coagulation tests is well recognized and mentioned in many laboratory manuals, possible contamination during sampling from indwelling lines is not cited.[8, 9]

Merenstein[10] reported that at least 4 ml of blood had to be withdrawn through the umbilical artery catheter lines they used (0.8-ml deadspace) to obtain an aPTT not altered by the continuous heparin flush used.[10] Earlier Bark[2] had reported that flushing the catheter with 50 ml of saline would eliminate the effect. Our prior experience has shown that repeatedly reproducible coagulation tests can be obtained providing that an adequate volume is withdrawn.[6, 11] This is contrary to the experience of Czapek[3] who found that withdrawing as much as 10 ml from the indwelling catheter prior to sampling did not obviate the heparin effect. However, the deadspace in his system was not stated.[3]

We had used Merenstein's data to justify a practice of withdrawing a volume of blood 5 times greater than the tubing deadspace volume (i.e., 10 ml with our lines) to obtain noncontaminated samples prior to this study. We were surprised at the normal results obtained when volumes equal to only the deadspace were withdrawn prior to sampling. The difference between our results and Merenstein's may be one of technique in that his study was essentially an in vitro study in which blood was taken from volunteers and infused through test catheters. Either larger deadspace or greater heparin flush concentration in their system may explain why Czapek was unable to obtain normal values even when discarding a 10-ml aliquot prior to sampling. Clearly our data show that discarding a much smaller volume will produce a normal value with our system.

In conclusion, heparin flush contamination of blood samples obtained from indwelling lines may produce false abnormally prolonged coagulation tests and care must be taken to avoid this. However, satisfactory blood samples for performing coagulation studies can be obtained from indwelling lines containing heparin flush solutions providing an adequate volume is removed prior to sampling. We recommend that although a volume equal to the deadspace volume of the lines through which the sample is being withdrawn would seem sufficient, that such an aliquot be twice the deadspace to be perfectly safe. Such a practice will eliminate the occasional abnormal result due to heparin flush contamination.

## REFERENCES

1. Rajoni K, Goetzman BW, Wennberg RP, et al: Effect of heparinization of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. Pediatrics 63:552–556, 1979
2. Bark CJ: Coagulation non-disease. N Engl J Med 282:1214, 1970
3. Czapek EE: Iatrogenic prolonged aPTT: a non-disease state. JAMA 227:1304, 1974
4. Hill JD, Dontigny L, deLaval M, et al: A simple method of heparin management during prolonged extracorporeal circulation. Ann Thorac Surg 17:129–134, 1974
5. Proctor RR, Rapaport SI: The partial thromboplastin time with Kaolin: a simple screening test for first stage plasma clotting factor deficiencies. Am J Clin Pathol 36:212–219, 1961
6. Ellison N, Ominsky AJ, Wollman H: Is protamine a clinically important anticoagulant? Anesthesiology 35:621–629, 1971
7. Bone RG, Francis BP, Pierce AK: Intravascular coagulation with the adult respiratory distress syndrome. Am J Med 61:585–589, 1976
8. Bowie EJW, Thompson JHJ, Didisheim P, et al: Mayo Clinic Laboratory Manual of Hemostasis. Philadelphia, WB Saunders Co, 1971, pp 65–77
9. Widman FK: Clinical Interpretation of Laboratory Tests. Philadelphia, FA Davis, 1973, pp 348–376
10. Merenstein GB: Heparinized catheters and coagulation studies. J Pediatr 79:117–119, 1971
11. Ellison N, Beatty CP, Blake DR, et al: Heparin rebound, studies in patients and volunteers. J Thorac Cardiovasc Surg 67:723–729, 1974

# letters TO THE EDITOR

## Modification of Oral Airway as a Bite Block

To the Editor:

When an oral endotracheal tube (ETT) is used, its guaranteed patency is essential. ETT obstruction results when either its internal diameter is plugged or external walls are compressed. The oropharyngeal (OP) airway, used to prevent external dental compression of the oral ETT, consists of three contiguous parts: a flange, a bite block, and a curved channel promoting an open pharyngeal contour by lifting the tongue off the posterior pharyngeal wall (Figure).[1] When the OP airway is used in situations requiring long term intubation, however, the curved pharyngeal channel produces considerable discomfort for the patient who is often conscious.

Modifying the OP airway by removing the curved pharyngeal channel (Dupaco oral airways, San Marcos, CA, modified by Eastern Anesthesia, Inc, Bensalem, PA) (Figure), not essential for airway patency in the intubated patient, yields a bite block with the advantages of the OP airway. A feature not present in a simple bite block is the flange which maintains the block's position relative to the lips and teeth. A heavy suture may be attached to the flange and taped to the patient's cheek for added safety (Figure). An additional benefit in using a cut OP airway as a bite block is the ease of suctioning through the air channel. Lastly this bite block with suction port may be positioned in the mouth for molar rather than canine compression for greater safety to dentition.

Alan Jay Schwartz, MD
*Assistant Professor of Anesthesia*
Rose Marie Dougal, CRNA
Kwang Won Lee, MD
*Assistant Professor of Anesthesia*
*Department of Anesthesia*
*The Children's Hospital*
*of Philadelphia*
*and University of Pennsylvania*
*Philadelphia, Pennsylvania 19104*

REFERENCE

1. Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment. Baltimore, Williams & Wilkins, 1975, pp 226–228

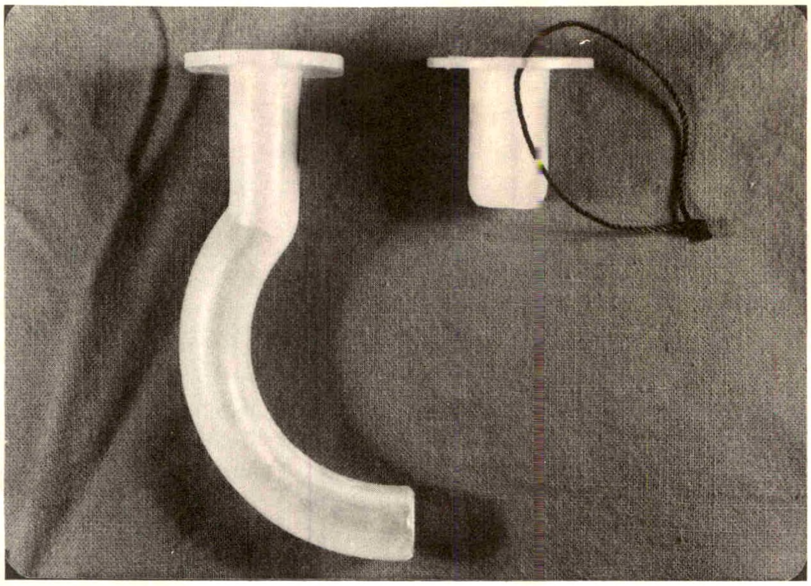


FIGURE. Oropharyngeal airway (left) and modified oropharyngeal airway (right) for use as a bite block.

## Rupture of Pressurized Plastic Bags

To the Editor:

Ready's suggestion[1] that a pressure-compensating automatic tourniquet be used to aid in the rapid intravenous infusion of large volumes of intravenous fluids and blood is an excellent example of adapting a mechanical device for a different labor-saving purpose. Others[2] have modified the standard wall oxygen pressure line for the same purpose.

The figure which accompanies Ready's article prompts this cautionary note. In Ready's figure the bag of fluid is bulging out over the top of the external pressure bag. We have experienced one occasion where the bulging seam of the plastic bag containing heparin solution split, resulting in a shower of solution on the operating field, the anesthesia machine, and the adjacent personnel. Fortunately, the bag was heparin, not a transfusion.

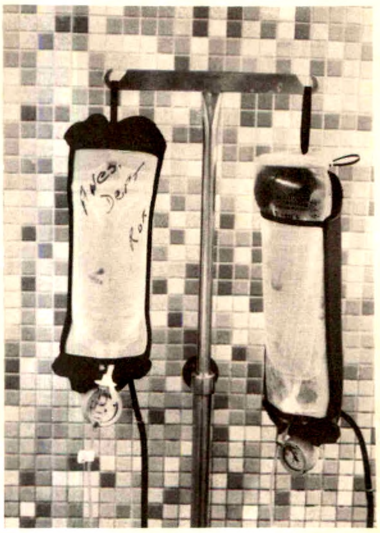


FIGURE. Correct-sized bags, but bag on right demonstrates use of external pressure bag that is too small, resulting in bulge.

Two steps will prevent this. First, the correct size bag must be used. Use of an external pressure bag designed to hold a 500-ml bag of blood or solution will invariably result in such a bulge when a 1000-ml bag of solution is placed within it. Second, even when the correct-sized bags are used, care must be taken to ensure that the top of the external pressure bag securely covers the top of the solution bag. In the accompanying figure the correct-sized bags were used. However, the bag on the right was deliberately misapplied to illustrate this possibility.

Alan Jay Schwartz, MD
*Assistant Professor of Anesthesia*
David R. Jobes, MD
*Assistant Professor of Anesthesia*
Norig Ellison, MD
*Associate Professor of Anesthesia*
*Department of Anesthesia*
*University of Pennsylvania*
*Philadelphia, Pennsylvania 19104*

### REFERENCES

1. Ready LR: An aid to rapid intravenous infusion. Anesth Analg 58:155, 1979
2. Waldman J, Rebane T: Self-regulating pressure valve for pumping blood. Anesthesiology 50:73–74, 1979

---

## V/Q Distribution in Adult Respiratory Distress Syndrome

The distribution of ventilation-perfusion ratios, as determined by the multiple inert gas elimination technique, was measured in 16 patients with the adult respiratory distress syndrome. In each case, the distribution of ventilation-perfusion ratios was bimodal. The upper mode consisted of units with normal ventilation-perfusion ratios that received a mean of 52% of the cardiac output. The lower mode, which received the remainder of the cardiac output, consisted of either pure shunt or shunt plus a small number of units with very low ventilation-perfusion ratios. The measured arterial $P_{O_2}$ and that predicted from the distribution of ventilation-perfusion ratios were closely correlated ($r = 0.93$), indicating that the hypoxemia was completely explained by the measured ventilation-perfusion inequality. In 12 patients, the effect of positive end-expiratory pressure on the distribution of ventilation-perfusion ratios was also determined. The addition of positive end-expiratory pressure uniformly resulted in a decrease in blood flow to the lower mode and an increase in the ventilation of unperfused alveoli. Increasing positive end-expiratory pressure also led to a uniform decrease in cardiac output. The authors conclude that the hypoxemia of the adult respiratory distress syndrome is caused by the presence of shunt or units of very low ratio of ventilation to perfusion and that positive end-expiratory pressure increases the arterial $P_{O_2}$ by decreasing the perfusion of unventilated lung. The mechanism of this decrease is yet to be defined. *(Dantzker DR, Brook CJ, Dehart P, et al: Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Respir Dis 120:1039–1052, 1979)*

# book REVIEWS

## Intravenous Anesthetic Agents, Current Topics in Anaesthesia, Volume 1, by J. W. Dundee, Chicago, Year Book Medical Publishers, 1979, 160 pp.

This book is the first of a new series intended to cover current topics in anesthesia. It is not intended to be a textbook on intravenous anesthetics but rather surveys what the author considered timely items at the moment the book was written. The author has had lengthy research experience and his personal involvement is reflected in the topics selected and the layout of the book.

The book is attractively packaged and the script seems well done considering the author's admitted haste (preface) to publish before the research is out of date. There are numerous graphs and tables which are well designed and add materially to the value of the book.

My major reservation about this book concerns the selection of topics covered. A major portion of the book is devoted to propanidid, Althesin, and Etomidate which are little used in clinical anesthesia and not approved for use in the United States and numerous other countries. On the other hand, balanced anesthesia techniques are discussed in a scant 12 pages. I realize these are reflections of the author's research experience; however, in my opinion this tends to make the book less attractive for a general clinical audience. The references cited are in the main from the British literature and are ample but not generous.

The section on benzodiazepine sedation-amnesia is particularly well done. The scope of the chapter obviously reflects the author's considerable expertise in this area. This chapter has numerous figures and tables which augment the presentation nicely.

One chapter by Dr. R.S.J. Clarke on hypersensitivity reactions is very detailed and has generous references. This topic which has not always received appropriate attention in the anesthesia community is well organized and presented in a manner that can be easily used by clinicians in anesthesia.

In summary, this book is recommended for those with an especial interest in intravenous anesthesia, remembering its content is distinctly colored by the author's research and clinical experience.

Albert L. Maduska, MD
Associate Professor
University of Tennessee
Memphis, TN

## Der alte Mensch in der Chirurgie, by J. Rehn, Berlin, Springer-Verlag KG, 1979, 245 pp.

This volume is a compendium of panel discussions and papers on management of the aged patient undergoing surgery, presented at the 145th Meeting of the Surgical Society of the Lower Rhine and Westphalia held recently in Bochum, West Germany, October 5–7, 1979.

Sixty-four presentations from 118 contributors from West Germany and Switzerland are organized in three sections. Section 1 is an interdisciplinary approach to the peculiarities of pre- and postoperative management, diagnostic procedures, special perioperative morbidity and risks, anesthetic management, and rehabilitation of surgical patients over 60 years of age. Section 2 deals in detail with the management of geriatric patients undergoing surgical procedures for fracture of the femur close to the hip joint. Section 3 is a compilation of papers on abdominal surgery in the aged patient.

The interdisciplinary management of aged patients is only briefly dealt with in this volume, although it is recognized as the key factor in decreasing perioperative morbidity and mortality and although it was claimed to be the central theme of this meeting. Those involved in pre- and postoperative care and anesthetic management of geriatric patients may find some useful hints and general principles in the first 74 pages; in-depth discussion, however, is not provided. Sections 2 and 3, consisting of detailed descriptions of surgical procedures and comparative mortality statistics, are addressed mainly to the surgeon and are of limited value for other specialists involved in perioperative care of the aged patient.

Edith R. Schmid, MD
Department of Anesthesiology
Mayo Clinic
Rochester, MN
Consultant, University Hospital
Zurich, Switzerland

## Modern Anesthesia in Dentistry, edited by A. Reyes-Guerra. Philadelphia, The Franklin Institute Press, 1977, 356 pp, $8.50.

This book has been submitted for

review two years after the publication date and the delay is understandable. Errors in spelling the names of common anesthetic drugs are readily apparent. Not only was Pentothal (thiopental sodium) misspelled, but it was reported to have been introduced after the start of World War II. All of this is found before page 1.

The first section of the book is titled Sophrology, a word not found in either a medical dictionary or in Webster's New Collegiate dictionary.

The book is a collection of papers presented at two International Congresses on Modern Pain Control that were sponsored by the Society for the Advancement of Anesthesia in Dentistry and were held in El Salvador in 1975 and Monaco in 1976. The quality of the material presented in this book is poor, as are the illustrations, two of which have the points of major interest identified with some oriental script.

Use of this collection of papers as an anesthesia textbook or reference book cannot be recommended.

Allan B. Gould, Jr, MD
Associate Professor of Anesthesia
Mayo Medical School
Rochester, MN

## BOOK NOTES

### **Dental Anesthesia and Analgesia,** by G. D. Allen. Baltimore, Williams & Wilkins, 1979, 446 pp, $24.95.

This second edition has four new contributors and several new chapters dealing with topics such as acupuncture, hypnosis, and the physiology and pharmacology of local anesthetics. Techniques of anesthesia for oral procedures are stressed and are often presented in a dogmatic manner.

The chapter on acupuncture leaves the reader with the impression that we clearly understand its mechanism and that there is no controversy related to its use and effectiveness. The section discussing problems associated with extremes of age is concerned with patients under three and those over the age of forty. Physiology and its relationship to the anesthetized patient is generally overlooked.

This book makes its major contribution by describing techniques and equipment that are unique to dental anesthesia.

### **Handbook of Medical Emergencies, Second Edition,** by J. H. Sanders and L. B. Gardner. Garden City, New York, Medical Examination Publishing Co, Inc, 1978, 362 pp.

As the title implies, this book is intended as a readily available initial resource of information for the management of medical emergencies. It is organized according to Internal Medicine subspecialties to maximize the convenience and speed in finding the situation one is looking for. As is the case with any such publication, it is representative of the state-of-the-art of about 2 years ago. The areas covered, although not encyclopedic, are covered appropriately.

### **Pre- and Postoperative Evaluation of Surgical Patients,** by T. Matsumoto, Garden City, New York, Medical Examination Publishing Co, Inc, 1979, 397 pp.

This book, written by and for surgeons, deals well with some of the factors in pre- and postoperative evaluation of patients in ten specific categories. There is no mention of anesthesia—the word is not found in the index—and there are many other specific areas not dealt with at all. The title would be more precise if it referred to "some surgical patients."

### **Atlas of Bedside Procedures,** edited by T. J. Vander Salm. Boston, Little, Brown & Co, 1979, 408 pp, $18.95.

This is a large format, well illustrated paper-bound atlas, which concisely describes how 40 different bedside procedures are performed by some members of the faculty of the University of Massachusetts Medical School at Worcester. Although one would not expect to be able to learn these procedures entirely from this atlas, it does provide a convenient, illustrated review, and a modest list of references regarding each procedure. Of interest to anesthesiologists would be the various vascular cannulation techniques, arterial puncture, intravenous regional anesthesia, cricothyroidotomy, and endotracheal intubation.

## BOOKS RECEIVED

**Acupuncture Manual, a Western Approach,** by L.S.W. Chu, S.D.J. Yeh, and D. D. Wood, New York, Marcel Dekker, Inc, 1979, 256 pp, $15.00.

**1979 Year Book of Anesthesia,** edited by J. E. Eckenhoff, A. J. Bart, E. A. Brunner, et al, Chicago, Year Book Medical Publishers, 1979, 351 pp, $23.75.

**Der Einflub von Anaesthetica auf die Kontraktionsdynamik des Herzens,** by K. J. Fischer. New York, Springer-Verlag, 1979, 278 pp, $43.50.

**Shock Trauma Manual,** by W. Gill and W. B. Long, Baltimore, Williams & Wilkins, 1979, 296 pp, $18.00.

**The Control of Chronic Pain,** by S. Lipton. Chicago, Year Book Medical Publishers, 1979, 134 pp.

**Analgesic Drugs,** by J. Parkhouse, B. J. Pleuvry, J. H. M. Rees. St. Louis, Blackwell Scientific Publications, 1979, 159 pp, $17.50.

**Zur Herzwirkung von Inhalationsanaesthetica,** by H. P. Siepmann, New York, Springer-Verlag, 1979, 66 pp, $21.80.

# I.A.R.S. MEMBERSHIP

## For Your In-training and Continuing Medical Education

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio founded in 1922 "To Foster Progress and Research in Anesthesia." To this end it performs two functions: (1) Publication of a monthly journal, ANESTHESIA and ANALGESIA; and (2) Sponsorship of annual scientific "Congress" meetings which meet the criteria for Category 1 credit toward the AMA Physicians Recognition Award.

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state or national anesthesia organizations.

## MEMBERSHIP - ASSOCIATE MEMBERSHIP

MEMBERSHIP is open to individuals with doctorate degrees, licensed to practice in the medical, dental, osteopathic or veterinary medicine professions (i.e., MD, MB, DDS, DMD, DO, DVM); and to individuals with doctorate degrees (Ph.D.) in any scientific discipline, engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP is open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists (RRT), or respiratory technicians (CRTT); and individuals completing accredited training programs as physician assistants-anesthesia, physician associates in anesthesiology, or as anesthesiologist's assistants.

DUES are $30 per year for U.S. Members and Associate Members, ($33 for all others) and include a subscription to ANESTHESIA and ANALGESIA. Members are also entitled to reduced registration fee at IARS annual scientific meetings.

## EDUCATIONAL MEMBERSHIP

EDUCATIONAL MEMBERSHIP is open to residents and fellows (interns) enrolled in anesthesiology training programs; registered nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician (anesthesiologist) assistants (associates); or students enrolled in respiratory therapist or technician training programs.

The official Education Membership blank must be certified by the applicant's training program director.

DUES are $30 for a two-year period, or $45 for a three-year period, and include a subscription to ANESTHESIA and ANALGESIA for a corresponding period. Educational Members are entitled to complimentary registration at IARS annual scientific meetings.

Application forms for Membership are available upon request to the Cleveland business office per application form below.

…………………………………………

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122, U.S.A.

Please send me application for: (____) Membership
(____) Associate Membership
(____) Educational Membership

(____) Please send ________ Educational Membership applications for students in anesthesia training.

______________________________
(Name)

______________________________
(Address)

______________________________
(City, State, Zip)

# A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

## Editorial Policies

Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

**Types of materials.** The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

**Peer review.** All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

**Legal and ethical considerations.** Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

**Editing.** All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

## Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

**Title Page.** The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

**Abstract and Key Words.** The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Define all abbreviations except those approved by the International System of Units.

*Key (indexing) terms.* Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract.

**Text.** The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

*Introduction.* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods.* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

*Results.* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

*Discussion.* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**References.** (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus*. Consult the "List of Journals Indexed," printed annually in the January issue of *Index Medicus*.

Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

*Journal*

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

    Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

    The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

    Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

*Books and Other Monographs*

3. Personal Author(s)

    Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

    American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

    Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

    Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

    National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

**Tables.** Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

**Illustrations.** Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of *original* drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 12.7 by 17.3 cm (5 by 7 in) but no larger than 20.3 by 25.4 cm (8 by 10 in). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them using paper clips. Do not bend figures.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with background.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, *regardless of authorship or publisher*, except for documents in the public domain.

For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Some journals publish illustrations in color only if the author pays for the extra cost.

**Legends for Illustrations.** Type legends for illustrations double spaced, starting on a separate page with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

**Abbreviations.** Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

# *International Anesthesia Research Society*

Publisher of ANESTHESIA and ANALGESIA

3645 Warrensville Center Road, Cleveland, Ohio 44122, U.S.A.

## I.A.R.S. EDUCATIONAL MEMBERSHIP

**SPONSORING ORGANIZATION:** The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio. It serves the Specialty in two ways: (1) By publication of a bimonthly journal entitled "Anesthesia and Analgesia"; and (2) By sponsorship of an annual scientific ("Congress") meeting in March of each year. The I.A.R.S. is independent of, and has no affiliation or membership-exchange arrangement with any other anesthesia society or association:

**PURPOSE OF EDUCATIONAL MEMBERSHIP:** To financially assist students in anesthesiology or anesthesia-related training programs by making available to them, during the effective term of their Educational Membership:

(1) A one-half price subscription to "Anesthesia and Analgesia" and
(2) Complimentary registration at the annual scientific meeting.

**WHO IS ELIGIBLE FOR EDUCATIONAL MEMBERSHIP:**

I Residents and Fellows (Interns) enrolled in training programs in the medical, osteopathic or dental professions;

II Nurses with a diploma or degree in nursing who are enrolled in nurse anesthesia schools;

III Students enrolled in programs leading to certification as Physician Assistants in Anesthesia/Anesthesiologist Assistants/Physician Associates in Anesthesiology; and

Students enrolled in programs leading to certification as Respiratory Therapists or Technicians.

**MEMBERSHIP TERMS AND COSTS:** There are two membership periods available. The applicable membership dues must be paid in full with the application (i.e., annual payments of $15 will not be accepted.)

**Two-Year Term—$30.00:** Individuals applying for this period should have at least 18 months remaining in their training program at the time of application:

**Three-Year Term—$45.00:** Individuals applying for this period should have at least 30 months remaining in their training program at the time of application.

**Note:** The Educational Membership term should not extend more than six months following the ending of the training program covered. To that end, I.A.R.S. may, at its option, enter memberships retroactively to conform. In such instances, back issues of the Journal will be sent so that all 2-year memberships include 12 Journals, and all 3-year memberships include 18 Journals.

**CANCELLATION OF MEMBERSHIP:** Educational Membership can be cancelled upon written request to the IARS, and return of membership card, if the member is no longer enrolled in the training program. Pro-rated refunds will be made at the discretion of the I.A.R.S.

**CONTINUATION OF MEMBERSHIP:** After completion of the Educational Membership period, and upon payment of membership dues then in effect, individuals in Category I will be automatically continued as Members; and individuals in Categories II and III will be automatically continued as Associate Members of the I.A.R.S.

**APPLICATION FORMS:** The official application form (or facsimile thereof) must be used in applying for this membership, and payment must be submitted with the application. Application forms are available from the Cleveland business office, address above.

## CLINICAL FACULTY POSITIONS OPEN 1980–1981 COLLEGE OF MEDICINE, KING FAISAL UNIVERSITY DAMMAM, SAUDI ARABIA

The expanding College of Medicine at King Faisal University is going into its sixth year of development and invites applications from qualified clinical faculty for the 1980–1981 academic year in:

*ANESTHESIOLOGY*

SALARIES are highly competitive and negotiable; comparable to other Saudi universities.

BENEFITS include free furnished housing, educational allowances, air tickets to and from Saudi Arabia once each year for a family of four, 60-day paid vacation in the summer, liberal overweight allowance.

Contracts are for one year and are renewable. Language of instruction is English.

Send *curriculum vitae* with current telephone number, and the names and addresses of three references to:

DR. TAWFIQ TAMIMI
Dean, College of Medicine
King Faisal University

c/o Saudi Arabian
Educational Mission
2221 West Loop South
Houston, Texas 77027

P. O. Box 2
Sunbury-on-Thames
Middlesex
England TW16 5JP

State University of New York
Upstate Medical Center

## STAFF ANESTHESIOLOGIST

Two positions at the rank of Assistant or Associate Professor will be available after January 1, 1980. Responsibilities include teaching, at the undergraduate, graduate and postgraduate levels, research and service. Four years of postgraduate training and eligibility for a New York license is required. An interest in regional anesthesia, pain therapy or intensive care advantageous but not essential. Highly competitive salary structure and excellent fringe benefits.

*Send curriculum vitae to:*

Howard L. Zauder, M.D., Ph.D.
Professor and Chairman
Department of Anesthesiology
State University of New York
Upstate Medical Center
Syracuse, New York 13210

## Cook County Graduate School of Medicine

announces

## SPECIALTY REVIEW COURSE IN ANESTHESIOLOGY

**May 11–16, 1980**

Alon P. Winnie, M.D., *Course Coordinator*
Chairman, Department of Anesthesia
Abraham Lincoln School of Medicine
University of Illinois

A six-day intensive review course which examines, in-depth, the clinical practice of Anesthesiology and the fundamental principles upon which it is based.

*A.M.A. Category I Credit: 54 Hours*

For further information and registration contact:

**Cook County Graduate School of Medicine**
**707 South Wood Street, Chicago, Illinois 60612**
**(312) 733-2800**

# classified ADVERTISING

## PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles has advanced clinical program for residents at the second and third year level of training. Also accepting applications from practicing anesthesiologists who wish to update their knowledge and proficiency. Positions available from 2 months to 1 year. Specialized year approved by the AMA. For further details contact:

George B. Lewis, Jr., MD
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, CA 90027
Phone (213) 662-1708

## MARYLAND:

The Maryland Institute for Emergency Medical Services Systems is seeking staff anesthesiologists with an interest and/or experience in critical care, trauma anesthesia and/or neuro-surgical anesthesia/critical care. MIEMSS is the 85 bed clinical center for trauma care and research in the State of Maryland. Teaching and research opportunities in a multidisciplinary setting are available. Salary negotiable, liberal fringe benefits. Send curriculum vitae to: Peter Chodoff, M.D., M.P.H., Chief, Critical Care/Anesthesia, Maryland Institute for Emergency Medical Services Systems, Baltimore, Maryland 21201

## TEXAS:

Board-certified or board-eligible anesthesiologist wanted to join department consisting of 2 board-certified anesthesiologists and 3 hospital employed CRNAs in 392-bed acute care hospital. Caseload consists primarily of general surgery, gynecology, minimal OB coverage, orthopedics and no cardiac surgery. Fee-for-service practice with generous first year salary guarantee. Texas malpractice rates are minimal and there is no state income tax. Our city has 170,500 people, low housing and utility costs, and a very modern medical center. For further details write to Box 2-80-D, c/o I.A.R.S.

## ANESTHESIOLOGIST

Position available for an Anesthesiologist in an active 460-bed general medical and surgical teaching hospital with strong affiliation with University of Missouri Medical School. Prefer candidate who is board certified or eligible. Licensure in any of the 50 states acceptable. Salary range $40,000 to $50,112 per year dependent on qualifications plus handsome bonus. Liberal fringe benefits. Call or write Warren P. Sights, M.D., Acting Chief of Staff, Harry S. Truman Memorial Veterans Hospital, 800 Stadium Road, Columbia, MO 65201, phone (314) 443-2511 ext. 6010. An Equal Opportunity Employer.

## MAYO FOUNDATION, DEPARTMENT OF ANESTHESIOLOGY—

Opportunities for advanced subspecialty training in cardiovascular and neuro-anesthesia, respiratory intensive care, and pain management are available to qualified candidates. Indepth training experience in one or more of these areas for periods of six months to two years may be arranged. For additional details, contact: Alan D. Sessler, M.D., Chairman, Department of Anesthesiology, Mayo Foundation, Rochester, Minnesota 55901.

## ANESTHESIOLOGIST—

70-physician multispecialty group in Western Kentucky, expanding to 80 plus physicians and surgeons; excellent opening in section of four M.D. anesthesiologists and nine C.R.N.A.'s; new 401-bed hospital opening December 1979; early partnership with incentive income distribution formula. Subspecialty interest in cardiovascular surgery and conductive anesthesia desirable but not mandatory. Contact: Medical Director, Trover Clinic, Madisonville, Kentucky 42431: 502-821-7171, Extension 205.

## ANESTHESIOLOGIST

Needed in small Minnesota city. Challenging cases, no open heart. Malpractice insurance paid. Salary first year, then buy-in. Reply to Box 9-79-H, c/o I.A.R.S.

## MISSOURI

Anesthesiologist wanted to join private group practice. 400-bed hospital with all specialties except open heart; little OB. Town of 100,000 with good schools, close airport, and good recreation. Excellent starting income, fringes, and potential. Reply to Box 7-79-A, c/o I.A.R.S.

## ANESTHESIOLOGISTS:

90 member multispecialty group adjacent to modern accredited 500 bed hospital seeks Board eligible or certified specialist to join associates; located in upper midwest university metropolitan area of 110,000; thirty-five minutes from superb clean lake region; associated with four year medical school; outstanding income; all specialties represented; will pay travel expenses for physician and spouse for interview. Write Box 3-80-A, % I.A.R.S.

## ANESTHESIOLOGIST:

Board certified with four years of real life clinical experience, familiar with critical care medicine, able to organize and upgrade a department's activities, current in all areas of anesthesia including cardiac, neuro and pediatrics, is seeking a private practice of anesthesia involving primarily supervision and teaching but also direct patient care and departmental function, in a growing community and a hospital with great potential. Send information to Box 11-79-A, c/o I.A.R.S.

## ANESTHESIOLOGISTS

Assistant & Associate Professors. Requirements: board certification or eligibility. Teaching & research experience, N.J. licensure. Competitive salary, faculty practice plan, large research laboratory. Send C.V. and names of 2 references to: Dr. Wen H. Wu, Professor & Chairman, Dept. of Anesthesiology, Medical Science Bldg., Rm. E538, or call (201) 456-5119. COLLEGE OF MEDICINE & DENTISTRY OF NEW JERSEY—New Jersey Medical School, 100 Bergen St., Newark, NJ 07103. Equal Opportunity/Affirmative Action Employer M/F.

# classified ADVERTISING

**ILLINOIS:**

Immediate openings for Board Certified/Eligible Anesthesiologists—Assistant and Associate Professors. Research Opportunities. Applications with Curriculum Vitae should be forwarded to: Dr. Donald Benson, University of Chicago, Department of Anesthesiology, 950 E. 59th Street, Chicago, Ill. 60637. AN EQUAL OPPORTUNITY EMPLOYER.

**VOLUNTEER ANESTHESIOLOGISTS NEEDED ABROAD**

Any interested candidates may obtain information on Voluntary Tours from MEDICO, a Service of CARE, 2007 Eye Street, N.W., Washington, D. C. 20006, telephone 202-223-2277.

**WEST VIRGINIA:**

Pain Clinic Fellowship commencing July 1, 1980 available to applicant with three years post graduate training in anesthesiology. Multi-disciplined Pain Clinic, seeing approximately 2,000 patients yearly, 25% of which are new patients. Clinic based on out-patient model with in-house beds available. Regular staff includes three anesthesiologists, a psychiatrist, and two clinical psychologists. Ancillary services include physical therapy, oral surgery and family practice. For further information contact Robert Bettinger, M.D., Director of Pain Clinic, Department of Anesthesiology, West Virginia University Medical Center, Morgantown, West Virginia 26506. Deadline for applications is April 1, 1980. An equal opportunity/affirmative action employer.

**ANESTHESIOLOGIST**

FMG currently doing a fellowship in Obstetric Anesthesia, looking for an exclusive private practice set up or one associated with a university, available August 1st, excellent references. Reply to BOX 3-80-B, % I.A.R.S.

*Rates for classified advertising: $3.00 per line, minimum 5 lines; box number ads $3.50 per line. Classified display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia, 3645 Warrensville Center Rd., Cleveland, OH 44122.*

McGILL UNIVERSITY
1980 ANNUAL REVIEW
COURSE IN
ANAESTHESIA
JUNE 2–6

An update of major clinical areas in anaesthesia directed towards residents, examination candidates and specialist anesthesiologists.

The distinguished guest faculty will include:

| | |
|---|---|
| Edward I. Eger, II | George A. Gregory |
| Norig Ellison | Carl C. Hug, Jr. |
| Donald C. Finlayson | Robert Kirby |
| M. Finster | John D. Michenfelder |
| Pierre Foex | Ronald D. Miller |
| Alison B. Froese | George Rodman |
| J. Kent Garman | |

This course is co-sponsored by the University of Vermont College of Medicine and is approved for AMA study credits, category 1.

FEES: $250.00 (canadian funds) or $215.00 (U. S. funds)
$150.00 (canadian funds) or $130.00 (U. S. funds)
(residents with letter from chief of service)

For further details write to:

The Secretary
Post-Graduate Board,
Royal Victoria Hospital
687 Pine Avenue, West
Montreal, Québec H3A 1A1

## *Los Angeles County University of Southern California Medical Center*

*is seeking Anesthesiologists at all levels*

to join a growing, forward-looking faculty. We are a large public medical center and primary teaching hospital of th[illegible]rsity of Southern California and a [illegible]erse clinical base: one of the mo[illegible]ing and sizeable in the natio[illegible]ns offered entail clinical and teach[illegible]n-sibilities with optional research [illegible] ities in obstetrics, neuro, respirato[illegible]d general anesthesia. Successful candi[illegible]s will possess a strong desire to teach [illegible] participate in the building of an outstanding clinical and educational program in anesthesia.

*Send C. V. to* **Glenn F. Gordon, M.D.**
**Department of Anesthesiology,**

**Los Angeles County/**
**University of Southern California**
**Medical Center**
1200 North State Street
Los Angeles, CA 90033

# INTRODUCING THE NEW "C" SERIES SPINAL TRAYS.

# THEY MAKE A POINT FOR SAFETY.

**There's a very important safety point in our new "C" Series spinal tray line: An exclusive 5 micron filter aspiration needle.**

This 19 ga. x 1½" needle contains a 5 micron particulate matter filter in its hub, which provides assurance against the inadvertent injection of glass ampule particles into the subarachnoid space.

It comes preattached to our clear 5 cc syringe, another safety feature which allows complete visualization of the drug mixture.

## PLUS, ALL THESE OTHER SAFETY AND CONVENIENCE POINTS, TOO.

**A light, clean spinal needle.** We use our own spinal needle with a metal hub and lightweight nylon tip stylet which is much less likely to dislodge.

And both cannula and stylet are match ground to guard against accidental tissue coring.

**Brand name drugs you can rely on,** with a variety of spinal anesthetics including Pontocaine,* Xylocaine** and Lyophilized Pontocaine; plus a choice of vasoconstrictors.

There's also a clean styrene basin with no styrofoam particles to flake off on your gloves; a sterilization indicator; three unique prep swabs and much more.

And the price is definitely a point in your favor.

Be sure to see our new "C" series.

For samples, just contact your Pharmaseal representative.

PHARMASEAL®
GLENDALE, CA 91201

*Pontocaine is Winthrop Laboratories' trademark
**Xylocaine is Astra Pharmaceutical Products' trademark

ISSN 0003-2999
vol. 59, no. 4 April 1980

Acc.
8.1.81

# Anesthesia and Analgesia

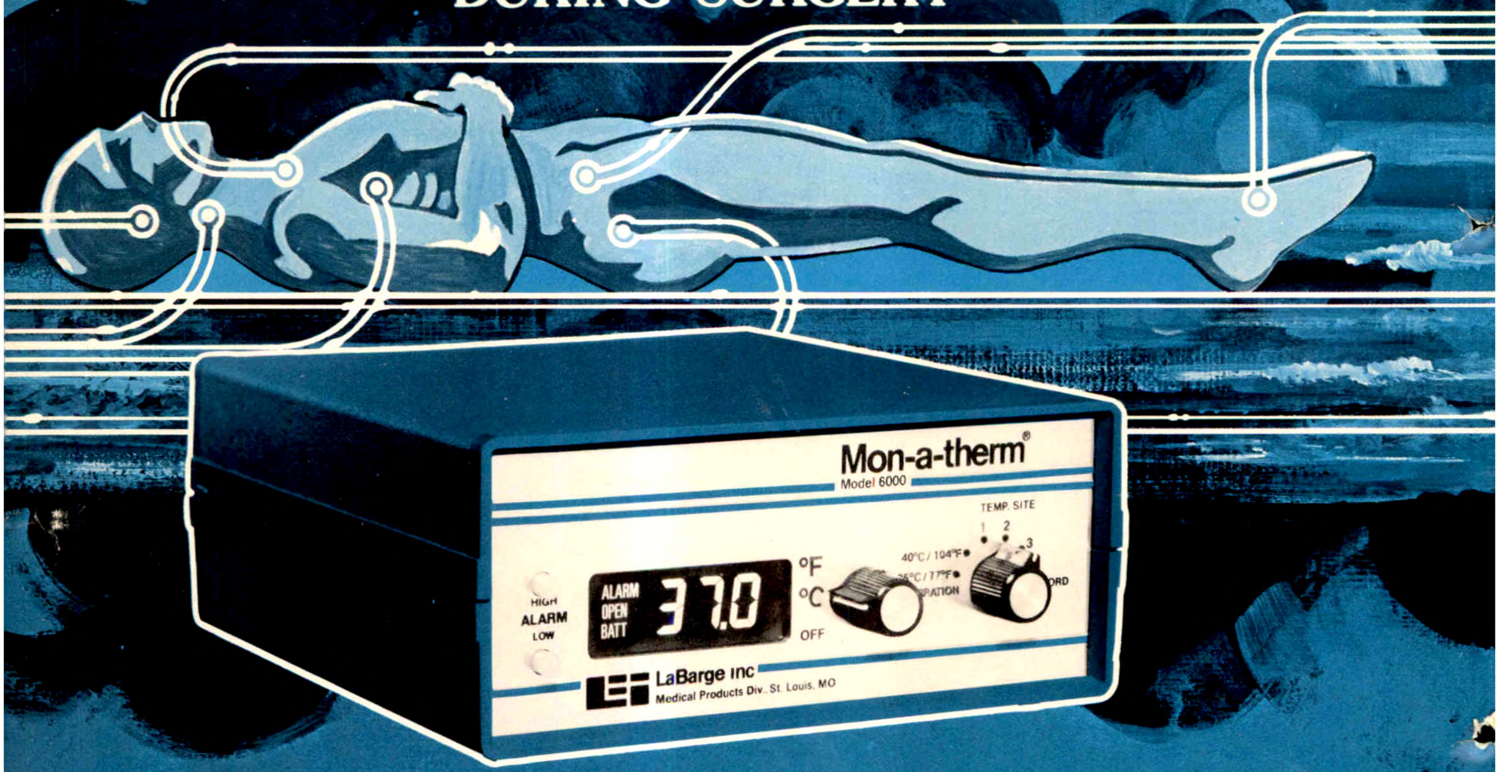
**Journal of the International Anesthesia Research Society**

OLDEST PUBLICATION IN THE SPECIALTY–
ESTABLISHED 1922

UNIVERSITY COLLEGE OF MEDICINE
LIBRARY

# A BREAK-THROUGH

## IN TEMPERATURE MONITORING DURING SURGERY



**Innovative features of the new Mon-a-therm® Model 6000 System:**

- ☐ Temp sites: multiple—monitor 3 sites simultaneously.
- ☐ Range: extended—for hyperthermia and hypothermia.
- ☐ Display: digital—°C or °F; backlighted LCD.
- ☐ Alarm: audio/visual—adjustable high-low limits.
- ☐ Calibration: confirmation—high-low calibration checks.
- ☐ Indicators: visual—alarm; open circuit; low battery.

Mon-a-therm® disposable temperature sensors:

- ■ skin ■ esophageal
- ■ rectal ■ tympanic
- ■ esophageal stethoscope with sensor
- ■ foley catheter with sensor
- ■ nasopharyngeal

**LaBarge Inc.**
**Medical Products Division**
**520 S. Jefferson Avenue**
**St. Louis, Missouri 63103**

**314 231-3400 in Missouri**
**800 325-3363 Toll Free**

# Anesthesia and Analgesia

Journal of the
International Anesthesia Research Society

3645 Warrensville Center Road
Cleveland, Ohio 44122
Telephones (216) 295-1124, 295-1130

## EDITORIAL BOARD

**Editor in Chief:**
**Nicholas M. Greene, M.D.,** New Haven, Connecticut

**Editors:**
**D. Ryan Cook, M.D.,** Pittsburgh, Pennsylvania
**Douglas B. Craig, M.D.,** Winnipeg, Manitoba
**E. Paul Didier, M.D.,** Rochester, Minnesota
**Ronald W. Dunbar, M.D.,** Atlanta, Georgia
**Alison B. Froese, M.D.,** Toronto, Ontario
**John P. Kampine, M.D.,** Milwaukee, Wisconsin
**David E. Longnecker, M.D.,** Charlottesville, Virginia
**John J. Savarese, M.D.,** Boston, Massachusetts
**N. Ty Smith, M.D.,** San Diego, California
**Robert K. Stoelting, M.D.,** Indianapolis, Indiana

**Book Review Editor:**
**E. Paul Didier, M.D.,** Rochester, Minnesota

**ANESTHESIA AND ANALGESIA** (ISSN 0003-2999) is published monthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, M.D., Bruce F. Cullen, M.D., E. Paul Didier, M.D., Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., B. B. Sankey, M.D., and Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris T. Nicholson, M.D., and T. H. Seldon, M.D.

**EDITORIAL CORRESPONDENCE** and manuscripts should be addressed to: **Nicholas M. Greene, M.D., Editor in Chief, Anesthesia and Analgesia, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: [203] 436-2887).** For information concerning preparation of manuscripts see "A Guide for Authors" published in each issue. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

**BOOKS FOR REVIEW** should be sent directly to the Book Review Editor, **E. Paul Didier, M.D., ℅ Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55901.**

**REPRINTS:** For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

**BUSINESS CORRESPONDENCE,** including subscription and membership payments, single issue purchases, change of address notices, and requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122 (Telephones: [216] 295-1124, 295-1130).**

**SUBSCRIPTION RATES:** United States and U.S. possessions, $30.00 per year (12 issues); all other countries, $33.00.

**MEMBERSHIP DUES (Including Journal Subscription):** United States and U.S. possessions, $30.00 per year; all other countries, $33.00 **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). **Educational Membership** (half the full price) available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only, upon completion of application including certification by applicant's program director.

**SINGLE ISSUES:** $5.50 each beginning 1979; $4.50 for years 1970–1978; $3.00 for years 1954–1969; $2.00 for years 1928–1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

**MAILING DATES:** Journals mailed 25th of month preceding issue date. Second class postage paid at Cleveland, Ohio and at additional mailing offices.

**CHANGE OF ADDRESS NOTICES:** Send to Cleveland business office as much in advance as possible to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable. POSTMASTER: Send address changes to Anesthesia and Analgesia, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

**ADVERTISING:** Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086 (Telephone: [609] 848-1000). Orders, contracts, and classified ad copy should be sent to the Cleveland office. Reproduction materials and inserts should be sent to Waverly Press, Inc., 300 Idlewild Avenue, Easton, Maryland 21601.

© 1980, International Anesthesia Research Society.

LIBRARY

# Anesthesia and Analgesia

## EDITORIALS

The Rate-Pressure Product in Clinical Anesthesia: Boon or Bane?—Barash PG, and Kopriva CJ ........ 229
Anesthesia Foundation Book Award—Greene NM ........ 232

## SCIENTIFIC ARTICLES

Correlates of Myocardial Oxygen Consumption when Afterload Changes during Halothane Anesthesia in Dogs—Wilkinson PL, Tyberg JV, Moyers JR, and White AE ........ 233
Myocardial Function during Halothane and Enflurane Anesthesia in Patients with Coronary Artery Disease—Delaney TJ, Kistner JR, Lake CL, and Miller ED Jr 240
Psychological Functioning after Halothane or Enflurane Anesthesia—Storms LH, Stark AH, Calverley RK, and Smith NT ........ 245
A Halothane-Induced Biochemical Defect in Muscle of Normal and Malignant Hyperthermia-Susceptible Landrace Pigs—Mitchell G, Heffron JJA, and van Rensburg AJJ ........ 250
Myocardial Reinfarction following Local Anesthesia for Ophthalmic Surgery—Backer CL, Tinker JH, Robertson DM, and Vlietstra RE ........ 257
Noninvasive Measurement of Pulmonary Gas Exchange during General Anesthesia—Noe FE, Whitty AJ, Davies KR, and Wickham BL ........ 263
Resistance to Breathing in Healthy Subjects following Endotracheal Intubation under Topical Anesthesia—Gal TJ, and Suratt PM ........ 270
Myotoxicity of Single and Repeated Injections of Mepivacaine (Carbocaine) in the Rat—Basson MD, and Carlson BM ........ 275
Risk of Hyperkalemia in Recipients of Kidneys Preserved with an Intracellular Electrolyte Solution—Hirshman CA, Leon D, Edelstein G, Brackebusch M, Casson H, Barry J, and Fuchs E ........ 283
Gastric Fluid Volume and pH after Fentanyl, Enflurane, or Halothane-Nitrous Oxide Anesthesia with or without Atropine or Glycopyrrolate—Stoelting RK ..... 287

## CLINICAL REPORTS

The Tracheal Tube Cuff Pressure Stabilizer and Its Clinical Evaluation—Kim J-M . 291
Postoperative Venous Air Embolism—Airola VM ........ 297

# Contents

April 1980
Volume 59/Number 4

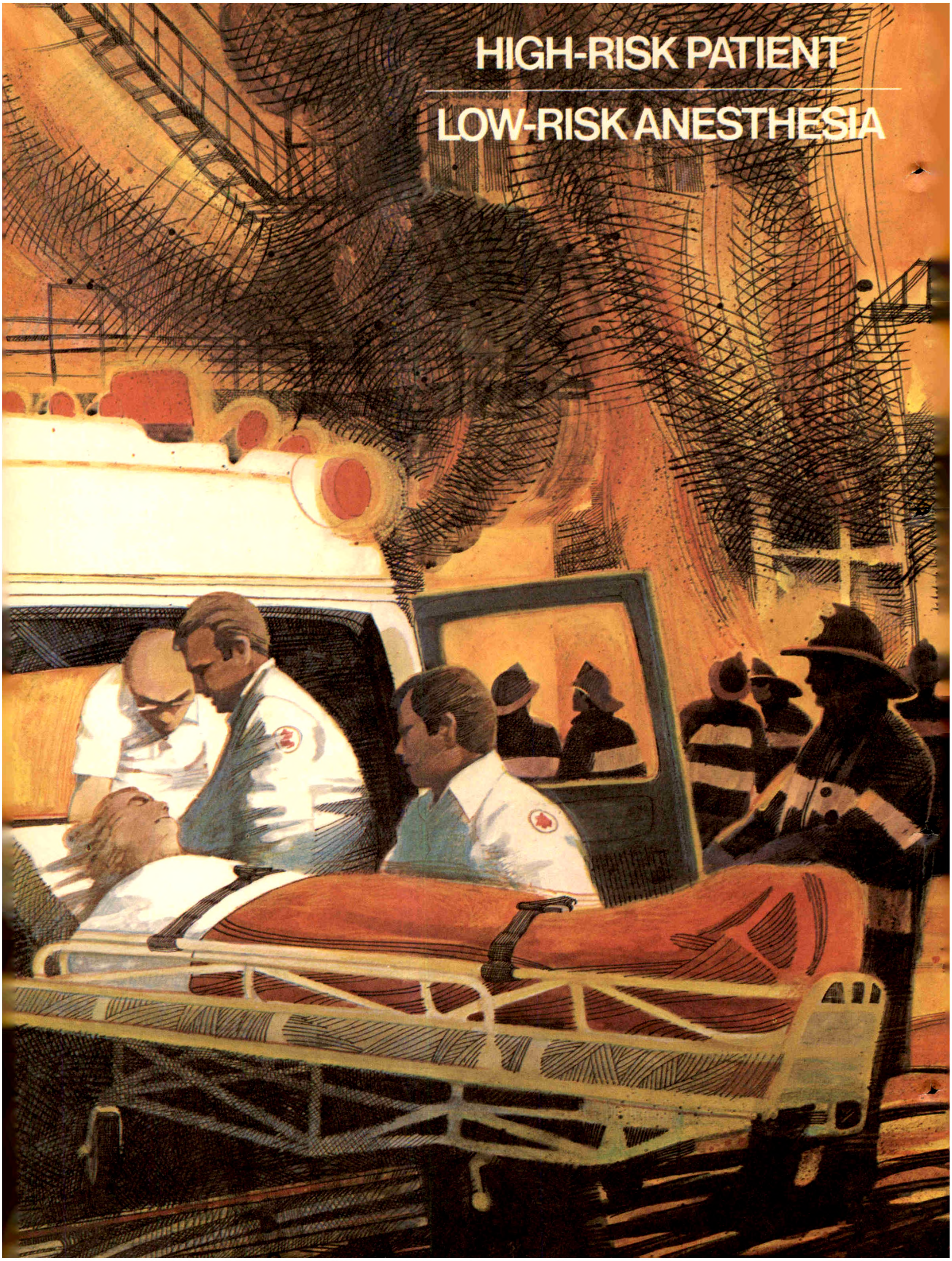
**Delayed Horner's Syndrome following Obstetric Extradural Block**—Hertz R, Chiovari CA, and Marx GF . . . . . 299
**Timolol-Induced Bradycardia**—Kim JW, and Smith PH . . . . . 301
**Cardiopagus in Neonatal Thoracopagus Twins: Anesthetic Management**—Bloch EC, and Karis JH . . . . . 304
**A Quantitative Neuromuscular Blockade Monitor**—Karis JP, Burton LW, and Karis JH . . . . . 308
**Postoperative Alopecia**—Patel KD, and Henschel EO . . . . . 311

## LETTERS TO THE EDITOR

**USP Oxygen Standards**—Wright WW . . . . . 314
**Purity of Oxygen, USP**—Rendell-Baker L . . . . . 314

## BOOK REVIEWS

**Controversy in Anesthesiology**—Eckenhoff JE . . . . . 316
**Shock Trauma Manual**—Gill W and Long WB . . . . . 316
**Modern Hospital**—Pütsep E . . . . . 317
**Nutritional Aspects of Care in The Critically Ill**—Richards JR, and Kinney JM (Eds) 317
**Coronary Heart Surgery**—Roskamm H, and Schmuziger M (Eds) . . . . . 318
**Outpatient Surgery**—Schultz RC (Ed) . . . . . 318
**Acute Care**—Tavares BM, and Frey R (Eds) . . . . . 319


HIGH-RISK PATIENT
LOW-RISK ANESTHESIA

# Ketalar®

## (ketamine hydrochloride injection, NF)

## Features you need...

Smooth, rapid onset of anesthesia, profound analgesia, IM or IV administration. Little risk of liver damage or buildup of tolerance following repeated procedures. Ketalar usually strengthens, rather than depresses, blood pressure, pulse rate and respiration. When necessary, it permits maintenance of unaided respiration because of minimal relaxation of skeletal muscles or laryngeal-pharyngeal reflexes.

## for the patients who need them

At either end of the age spectrum, the pediatric or geriatric patient. The patient in shock, or with shock potential. Patients in whom establishing an IV route of administration is difficult. The burn patient requiring repeated dressing changes. Patients requiring manipulative or diagnostic procedures. The debilitated patient. The emergency patient who may not have an empty stomach.

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

**SPECIAL NOTE**

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA-SHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

**CONTRAINDICATIONS**

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

**WARNINGS**

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemcially incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

***Usage in Pregnancy:*** Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

**PRECAUTIONS**

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. **The incidence of emergence reactions may be reduced** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

**ADVERSE REACTIONS**

*Cardiovascular:* Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

*Respiration:* Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

*Eye:* Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

*Psychological:* (See Special Note).

*Neurological:* In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

*Gastrointestinal:* Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

*General:* Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

**HOW SUPPLIED**

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-458 -15 – Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-458 -12 – Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-458[illegible]-10 – Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.
N 0071-458[illegible]-08 – Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.

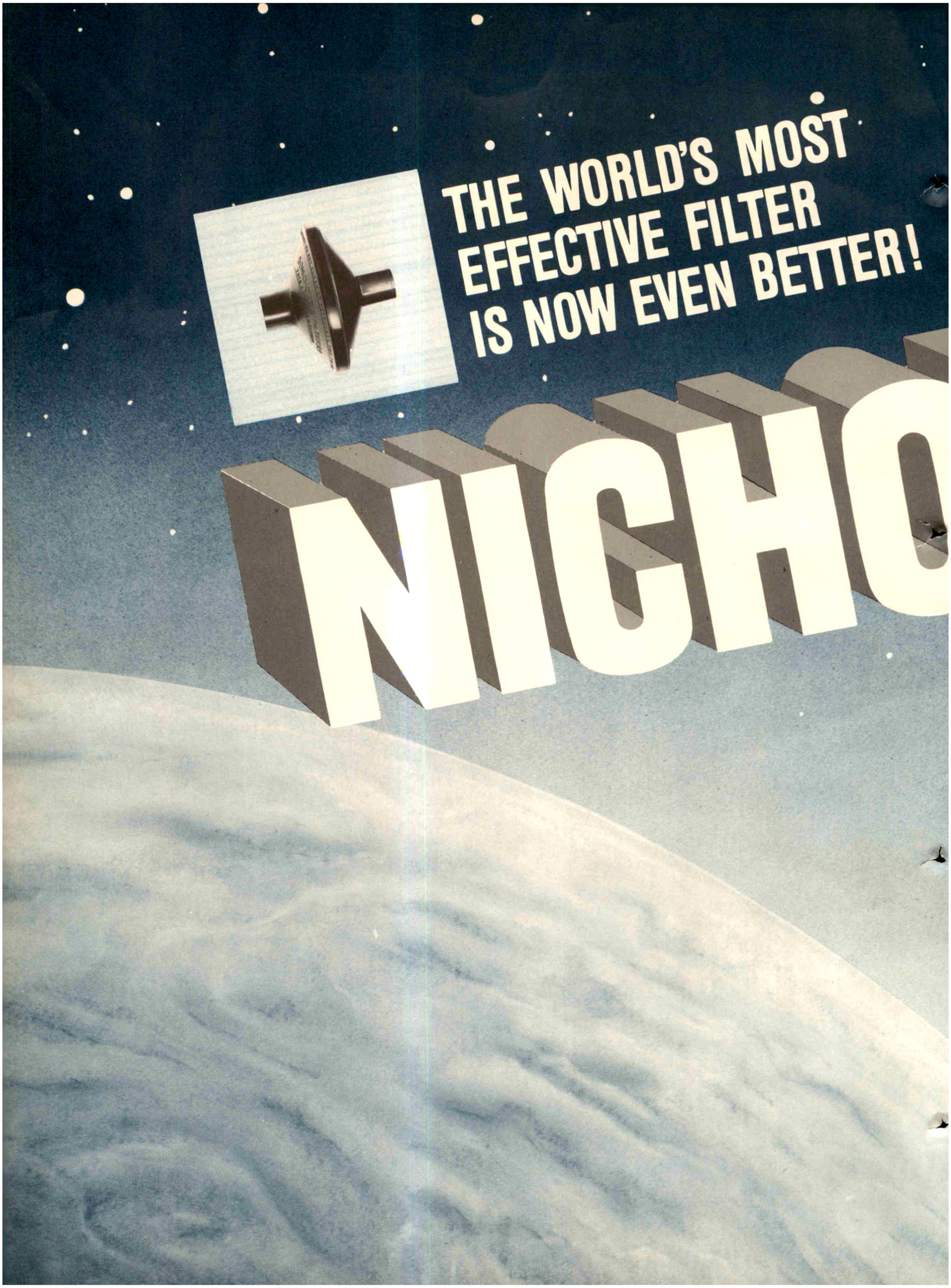
**SG**

**PARKE-DAVIS**

*PARKE-DAVIS*
*Division of Warner-Lambert Company*
*Morris Plains, NJ 07950*

©1979 Warner-Lambert Company

PD-JA-2645-1-P (4-79)


THE WORLD'S MOST
EFFECTIVE FILTER
IS NOW EVEN BETTER!
NICHO

# LES II T.M.

## THE 2nd GENERATION

**PROVEN EFFECTIVE: 99% B.F.E.**

Features an all new internal filter structure with hermetic tri-gard locking device for added structural integrity and fail-safe performance.

- ✓ The unique electrostatic filter works like a magnet; not just a strainer.
- ✓ Bacterial and Viral retentive. Biological testing proves it effectively stops all pathogens including Pseudomonas aeruginosa and Staphylococcus auereus.
- ✓ Only filter documented 99% reliable against all organisms regardless of size.
- ✓ New hydrophobic reticulated chambers produce unique capillary action that diverts excessive condensate and rainout.
- ✓ Encapsulated filter media for maximum filter integrity and improved performance.
- ✓ Non-pleated filter media.
- ✓ Protection against biological and inorganic contamination or migration.
- ✓ Actual Biological Filtration Efficiency (B.F.E.) documentation measures effectiveness & reliability.
- ✓ Hydrophobic treatment permits use under high relative humidity.
- ✓ Fail-safe against filter dislodgement.
- ✓ Virtually leak proof.
- ✓ Multi-directional. Can be installed or interposed anywhere upstream of humidification device.
- ✓ Low airflow resistance eases patient breathing.
- ✓ Eliminates potential compliance problems. Will not backwash if accidentally reversed.

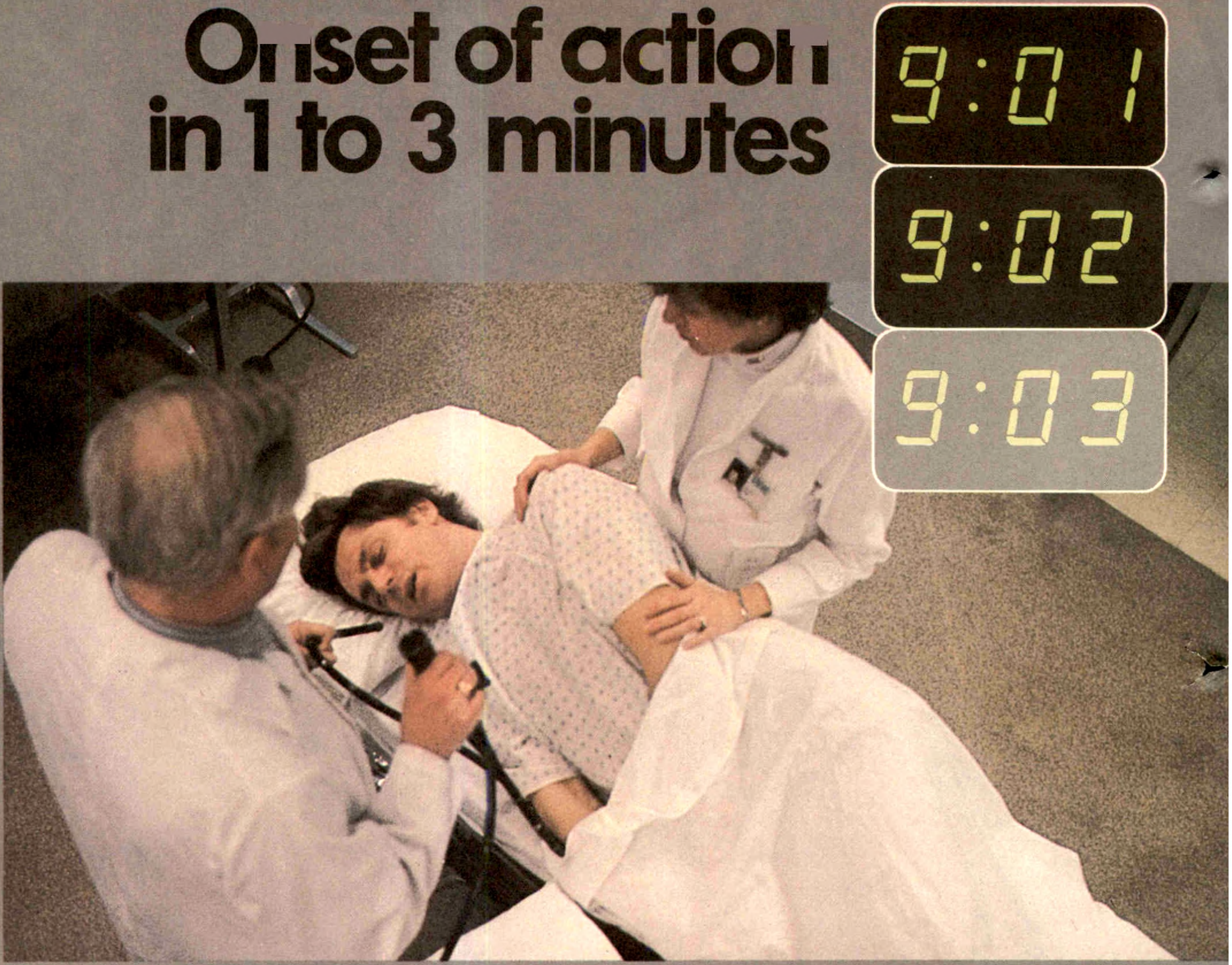
Don't settle for the outdated window screen technology of porosity type filters.

Demand state-of-the-art effectiveness and reliability. Evaluation samples and documentation available upon request. For private label or international sales information call Ray Sheppard, (305) 652-2365.
For hospital or dealer sales call J. M. Alvarez, (305) 596-6878.

**K&G**

K&G Healthcare Industries, Inc.
5373 N.W. 36th Street
Miami Springs, FL 33166

# Onset of action in 1 to 3 minutes



## for a calmer, relaxed patient

When impending surgery causes high levels of anxiety, administering Valium (diazepam/Roche) I.V. can be a valuable pre-anesthetic maneuver. Within 3 minutes, Injectable Valium reaches peak blood levels, promptly relieving patients of excessive apprehension.

## Diminished recall

Within three minutes of injection, Valium I.V. produces anterograde amnesia. This important property allows most patients to virtually forget induction of anesthesia, passage of endoscopic instruments and similar distressing events. However, when required, patients usually can respond to directions—an important advantage in surgery conducted under regional anesthesia or in procedures such as endoscopy and cardioversion.

## Permits reduction of analgesic dosage

When Valium I.V. is used with a narcotic analgesic, the dosage of the narcotic can and should be reduced by at least one-third. In some cases the use of a narcotic may not be necessary.

## Predictable duration of action

Because the sedating effect of Valium (diazepam/Roche) I.V. is of predictable duration, patients can be released only a few hours after minor surgery or short-term diagnostic procedures. By then, alertness is restored, since post-procedural drowsiness is minimal and short-lived. As with most CNS-acting drugs, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving.

ROCHE®

# Hours later ready to be released

Injectable

## Valium® I.V.

diazepam/Roche Ⓒ IV

A pattern of antianxiety action that meets outpatient needs

**Please see summary of product information on following page.**

# New/Improved

# Tel-E-Ject®

## 10-mg Disposable Syringe (5 mg/ml)

scale on both sides
of barrel eases
visibility during
administration

# Injectable

# Valium® I.V.

## diazepam/Roche

10-ml vials } 5 mg/ml
2-ml ampuls }

**Please consult complete product information, a summary of which follows:**

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy.

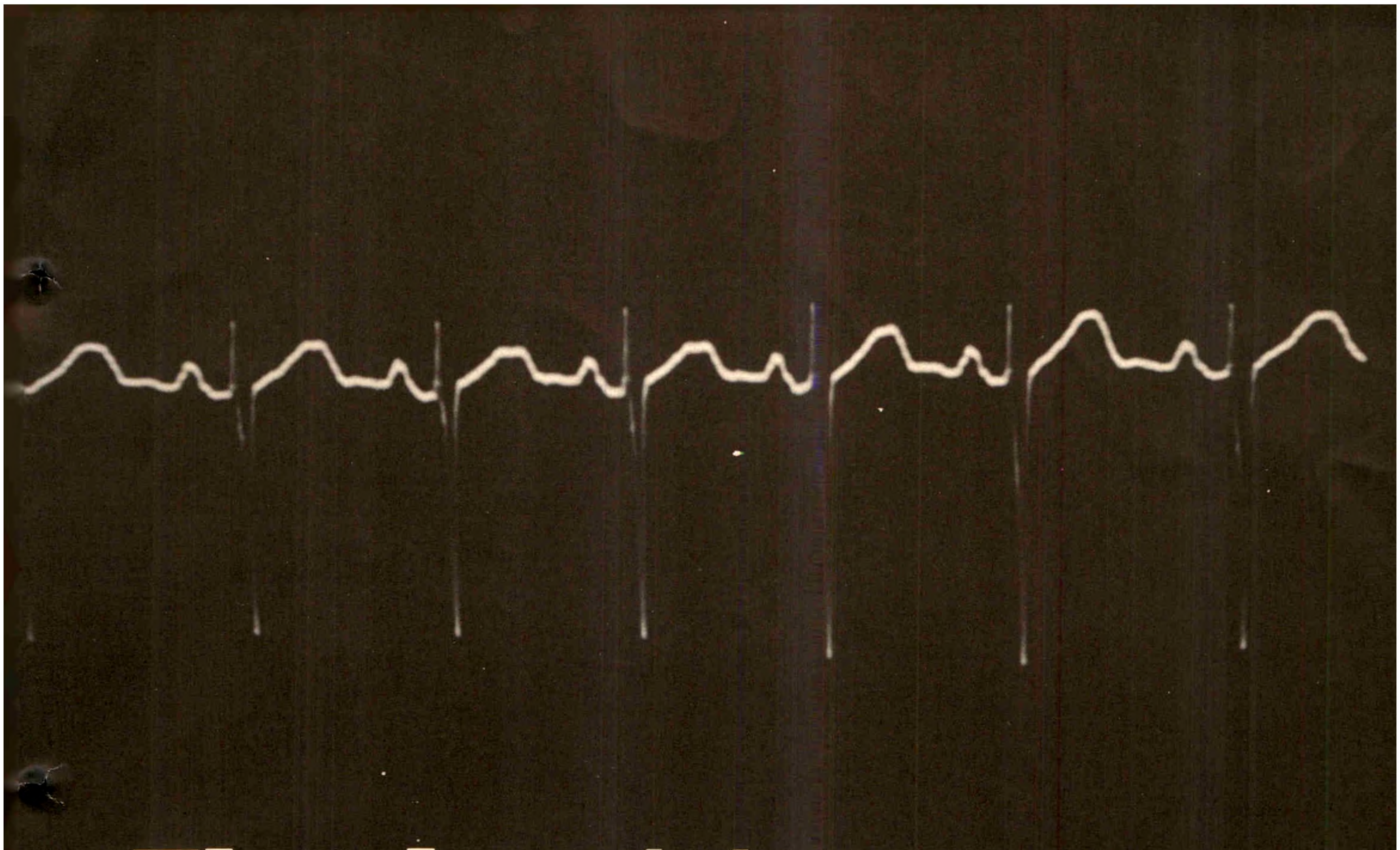
If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE®
ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110



# The best trace... in the least time.

The trace shown here is what you can expect each time you monitor with NDM electrodes.

You will see a high amplitude signal with a narrow base line.

And you won't have to wait long for that remarkably narrow base line to stabilize. Monitoring can begin as soon as you have connected the leadwires.

Trace quality won't deteriorate during long procedures, or as a result of defibrillation, either. (Repeated 400 watt-second charges won't polarize NDM electrodes. A stable trace returns to your monitor within one second.)

With their ultra-low heating characteristics, NDM electrodes also reduce the chance of an electrosurgical mishap causing RF burns at ECG electrode sites.

There is an NDM electrode just right for your OR, including one with a special adhesive to resist contact loss from spilled fluids or prep solutions.

If you are making do with one of the thirty or so other electrode brands, please consider this: *Over half of the monitoring done in the U.S. is done with NDM electrodes.*

A trial will convince you, and it's yours for the asking. Returning the coupon can be the first step toward reducing your electrode problems.

Thank you

**NDM®** NEW DIMENSIONS IN MEDICINE

Distributed by American Hospital Supply

NDM Corporation, Dept. D
3040 E. River Road
Dayton, Ohio 45439

☐ Please have a representative contact me.
☐ Send information about NDM electrode systems.

Name: ____________________ Title: __________

Hospital: ____________________ Dept.: __________

Address: ______________________________

City: __________ State: __________ Zip: __________

Phone: ____________________ Ext.:

SIEMENS

New self-regulating hygroscopic humidifier for anesthesia and intensive care

The Servo Humidifier, a new unique hygroscopic humidifier, is capable of maintaining 80% r.h. at 37 °C in the trachea of mechanically ventilated patients, receiving totally dry respiratory gases. A conventional heat and moisture exchanger, will maintain only 55% at 37 °C.

In most clinical applications the hygroscopic Servo Humidifier replaces the conventional bubble type, reservoir humidifier, thus eliminating the need for an external water and electrical supply.

The hygroscopic Servo Humidifier eliminates condensation in the patient tubing circuit and can be used with all mechanical ventilators and most anesthesia gas machines.

Contact your local Servo Ventilator distributor for our fullcolor Servo Humidifier folder and further information or write directly to us.

Servo Humidifier 150 and 151

I would like to have more information about the Servo Humidifier

Name ______________________________

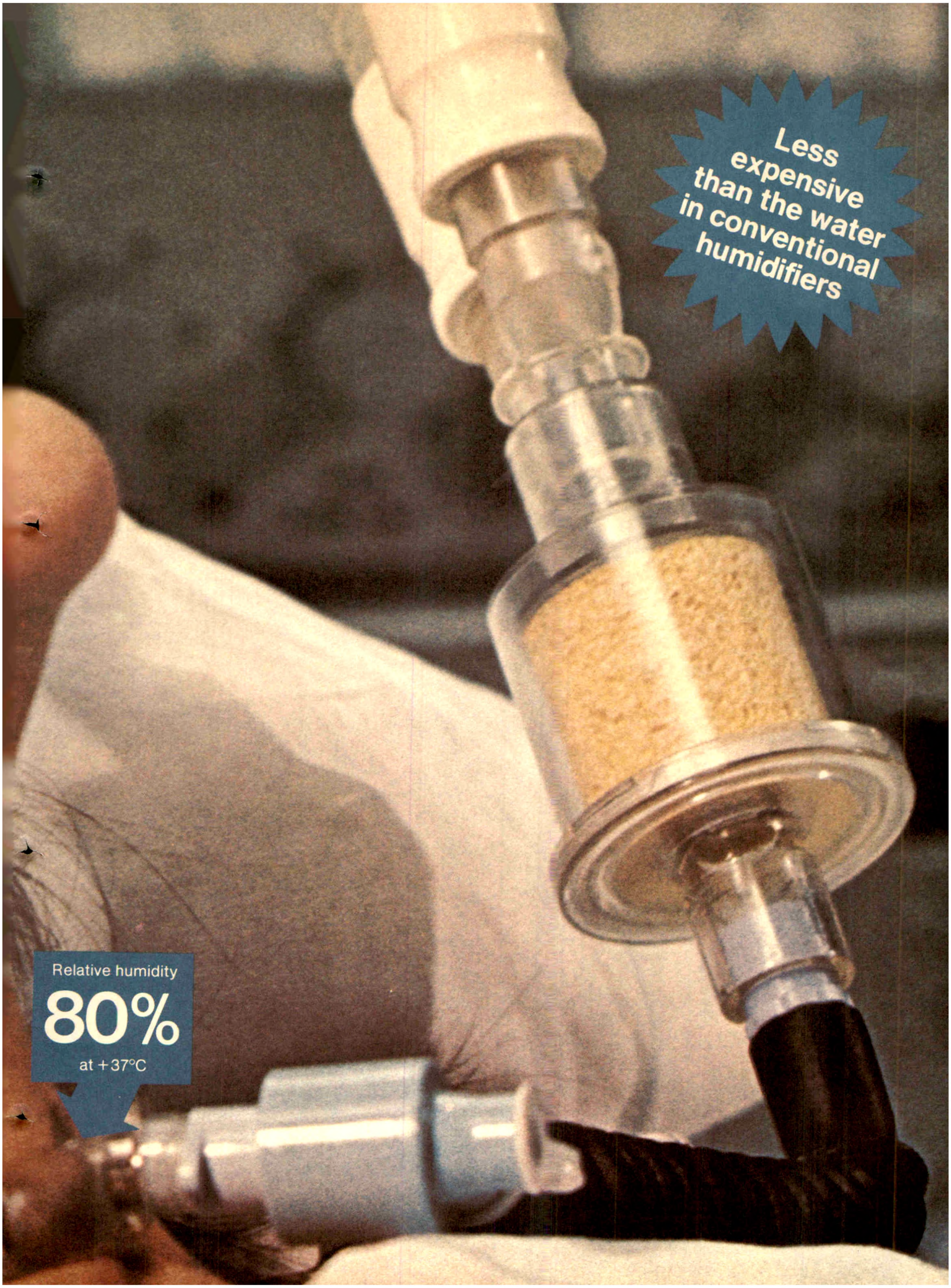
Position ______________________________

Hospital ______________________________

Address ______________________________

SIEMENS-ELEMA
Siemens-Elema Ventilator Systems
1765, Commerce Drive, Elk Grove Village, Illinois 60007, Telephone: (312)981-4940

For countries outside U.S.:
Siemens-Elema AB, Ventilator Division, S-17195 Solna, Sweden


Less expensive than the water in conventional humidifiers
Relative humidity
80%
at +37°C

YOU KNOW THE POSITIVE SIDE OF
NARCOTIC-SUPPLEMENTED ANESTHESIA...
TITRATES THE RESPIRATORY DEPRESSION OU

# NARCAN®

## naloxone HCl

## NEUTRALIZES THE NEGATIVE

### NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

### Useful when narcotic/$N_2O$ anesthesia is employed

### Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism

The duration of activity of some narcotics may exceed that of NARCAN®. Observe the patient closely and give repeat doses of NARCAN® if needed.

### Also available, NARCAN® NEONATAL naloxone HCl

Please see next page for complete prescribing information.

**Endo Laboratories, Inc.**
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, New York 11530

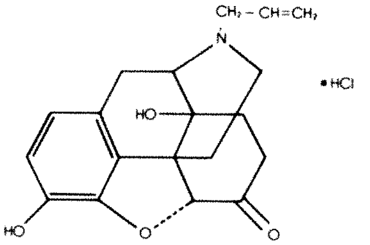
DU PONT
REG. U.S. PAT & TM OFF

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088.

## OF NARCOTIC-SUPPLEMENTED ANESTHESIA

# NARCAN®
## naloxone HCl

**DESCRIPTION** NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

**ACTIONS** NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

**INDICATIONS** NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

**CONTRAINDICATIONS** NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

**WARNINGS** NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

**Usage in Pregnancy** Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

**PRECAUTIONS** In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

**ADVERSE REACTIONS** In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

**DOSAGE AND ADMINISTRATION** NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

**USAGE IN ADULTS Narcotic Overdose—Known or Suspected** The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

**Post Operative Narcotic Depression** For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

**USAGE IN CHILDREN Narcotic Overdose—Known or Suspected** The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

**USAGE IN NEONATES Narcotic-induced depression** The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

**HOW SUPPLIED** 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

**ANIMAL PHARMACOLOGY AND TOXICOLOGY** In the mouse and rat the intravenous $LD_{50}$ is 150 ±5 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the $LD_{50}$ (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

**Endo Laboratories, Inc.**
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT
REG U.S. PAT & TM OFF

EDO-050N

May, 1977

# Tap our resources

Provide practical learning experience in your training sessions with realistic Life/form® products from Nasco. The **free** Health Care Educational Materials Catalog describes exceptional selection of anatomical replicas and simulators. Molded from actual organs in lifelike vinyl, they offer both visual and tactile learning experiences.

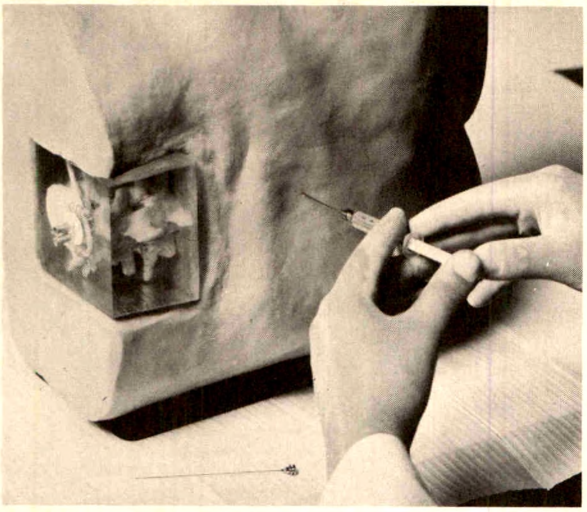
The spinal injector simulator, for example, features a clear plastic window at the top of the model. It displays the L1 and L2 sections of the vertebral column, as well as other anatomical details. With the functional portion, students get the "actual feeling" for performing all types of spinal injections.

Catalog includes many other simulation devices, models, charts and visual media for all areas of medical education. Send for your free copy today. Write Dept. RA-804.

**Free Phone Order Service 1-800-558-9595**
**In Wisconsin 1-800-242-9587**

**Nasco**

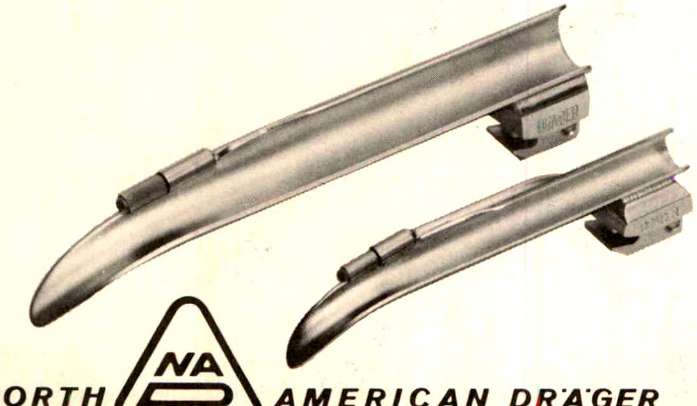
Fort Atkinson, WI 53538 Modesto, CA 95352



NASCO
HEALTH CARE
EDUCATIONAL
MATERIALS

# PHILLIPS
## LARYNGOSCOPE BLADES
### Now Two Sizes
### Adult and Pediatric

The Phillips Blade by North American Drager combines into one blade many features of the Jackson-Eversole Blade and the Miller Blade. The light of the Phillips Blade is on the left side to afford excellent visualization of the Larynx and allows room for passing a tube along the blade for difficult intubations.

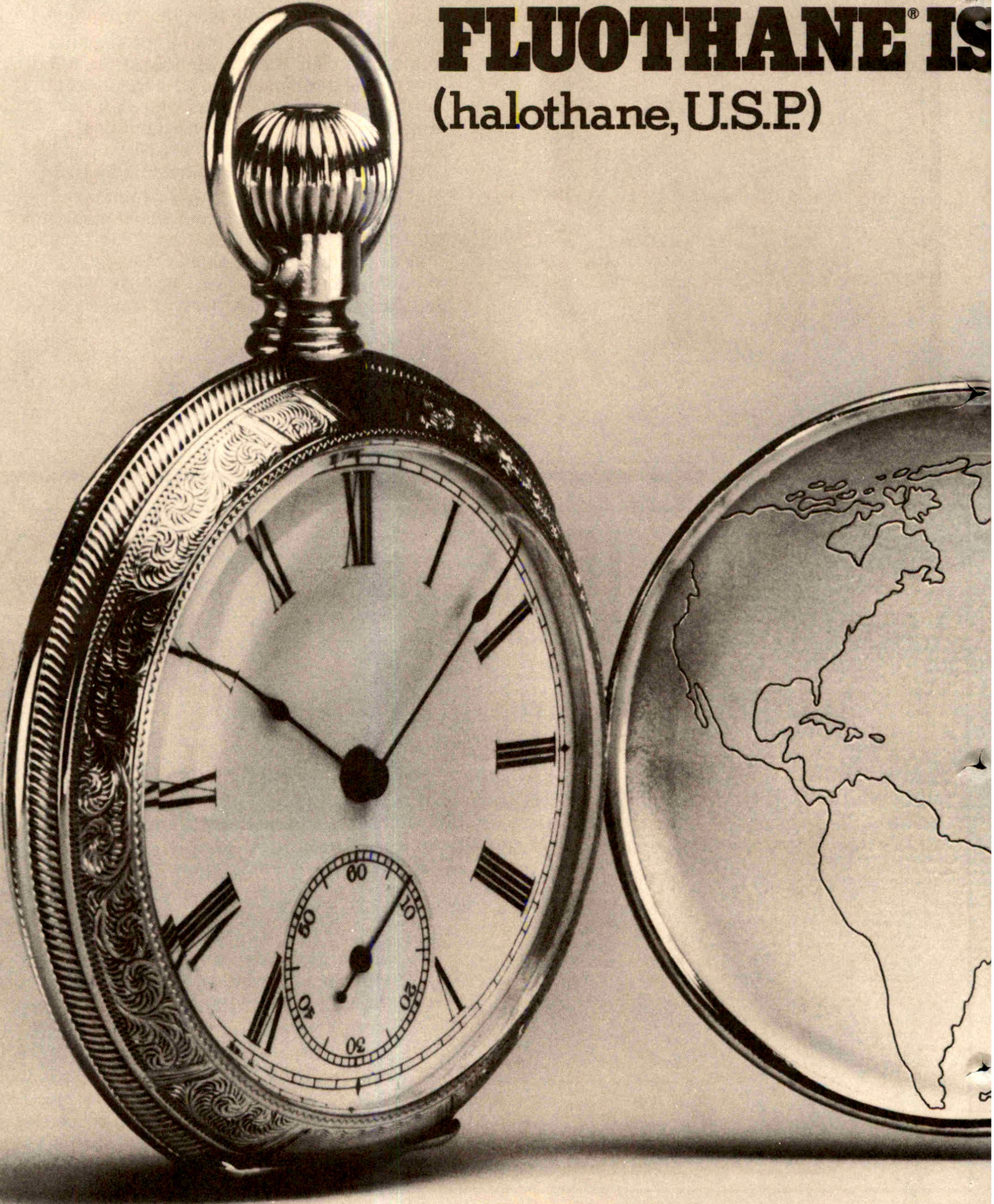


The Adult Blade has been found adequate for the largest adults encountered; the small tip, in addition makes it adaptable for use in children as small as 2 or 3 years of age. The Pediatric Blade is a replica of the Adult Blade that has been reduced in all aspects of shape and size, including thickness of the metal. It can be used in patients from newborn to about 4 years of age.

**NORTH AMERICAN DRÄGER**
*148B QUARRY ROAD, TELFORD, PA 18969*

# EVERY TWO SECONDS FLUOTHANE® IS

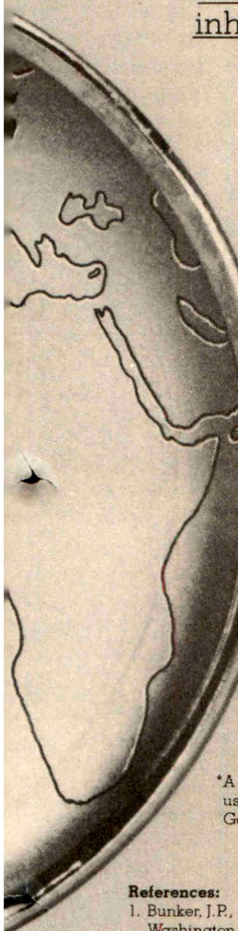
(halothane, U.S.P.)



# THE WORLDWIDE CHOICE.

## ver 500 million administrations throughout the world. ell over 125 million administrations in the nited States alone.

mewhere in the world—every two seconds—someone makes another decision use FLUOTHANE® (halothane, U.S.P.). And for good reasons:



☐ FLUOTHANE has been more widely investigated than any other inhalation anesthetic.

☐ The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and... the overall safety record of the anesthetic was excellent."[2]

☐ FLUOTHANE "... is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]

☐ FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.

☐ And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

**References:**

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology *43*:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

Ayerst®
Ayerst Laboratories
New York, N.Y. 10017

# the most widely used inhalation anesthetic in the world

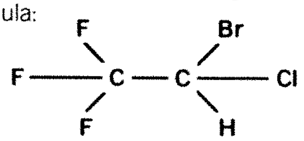
# FLUOTHANE®

## (halothane, U.S.P.)

## for a wide variety of techniques and procedures in patients of all ages

*(Complete text of package circular.)*

**Description.** FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

**Actions.** FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

**Indications.** FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

**Contraindications.** FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

**Warnings.** When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

*Usage in Pregnancy.* Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

**Precautions.** The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

**Adverse Reactions.** The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

**Dosage and Administration.** FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

**How Supplied.** No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P. stabilized with 0.01% thymol (w/w).

**Ayerst.** Ayerst Laboratories
New York, N.Y. 10017

7197/80

# I.A.R.S. MEMBERSHIP

## For Your In-training and Continuing Medical Education

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio founded in 1922 "To Foster Progress and Research in Anesthesia." To this end it performs two functions: (1) Publication of monthly journal, ANESTHESIA and ANALGESIA; and (2) Sponsorship of annual scientific "Congress" meetings which meet the criteria for Category 1 credit toward the AMA Physicians Recognition Award.

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state or national anesthesia organizations.

## MEMBERSHIP - ASSOCIATE MEMBERSHIP

MEMBERSHIP is open to individuals with doctorate degrees, licensed to practice in the medical, dental, osteopathic or veterinary medicine professions (i.e., MD, MB, DDS, DMD, DO, DMV); and to individuals with doctorate degrees (Ph.D.) in any scientific discipline, engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP is open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists (RRT), or respiratory technicians (CRTT); and individuals completing accredited training programs as physician assistants-anesthesia, physician associates in anesthesiology, or as anesthesiologist's assistants.

DUES are $30 per year for U.S. Members and Associate Members, ($35 for all others) and include a subscription to ANESTHESIA and ANALGESIA. Members are also entitled to reduced registration fee at IARS annual scientific meetings.

## EDUCATIONAL MEMBERSHIP

EDUCATIONAL MEMBERSHIP is open to residents and fellows (interns) enrolled in anesthesiology training programs; registered nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician (anesthesiologist) assistants (associates); or students enrolled in respiratory therapist or technician training programs.

The official Education Membership blank must be certified by the applicant's training program director.

DUES are $30 for a two-year period, or $45 for a three-year period, and include a subscription to ANESTHESIA and ANALGESIA for a corresponding period. Educational Members are entitled to complimentary registration at IARS annual scientific meetings.

Application forms for Membership are available upon request to the Cleveland business office per application form below.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122, U.S.A.

UNIVERSITY COLLEGE OF MEDICINE
LIBRARY

Please send me application for: (____) Membership
(____) Associate Membership
(____) Educational Membership

(____) Please send ________ Educational Membership applications for students in anesthesia training.

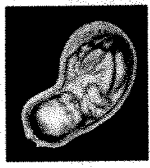
(Name)

(Address)

(City, State, Zip)

See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

# More protection for the newborn



# Marcaine® hydrochloride

brand of
## bupivacaine hydrochloride

with or without epinephrine 1:200,000

**Indications:** Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

**Contraindication:** Marcaine is contraindicated in patients with known hypersensitivity to it.

**Warnings:** RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

*Usage in Pregnancy.* Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

**Precautions:** The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

**Adverse Reactions:** Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

*Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

*Treatment of Reactions.* Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

**References:**

1. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.
2. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
3. Scanlon JW, Ostheimer GW, Brown WV, et al: Neurobehavioral responses of newborns after maternal epidural anesthesia with bupivacaine. *Abstracts Annual Meeting, Soc. Obstet. Anesth. and Perinat.*, 1974.

BREON
**BREON LABORATORIES INC.**
90 Park Avenue, New York, N.Y. 10016

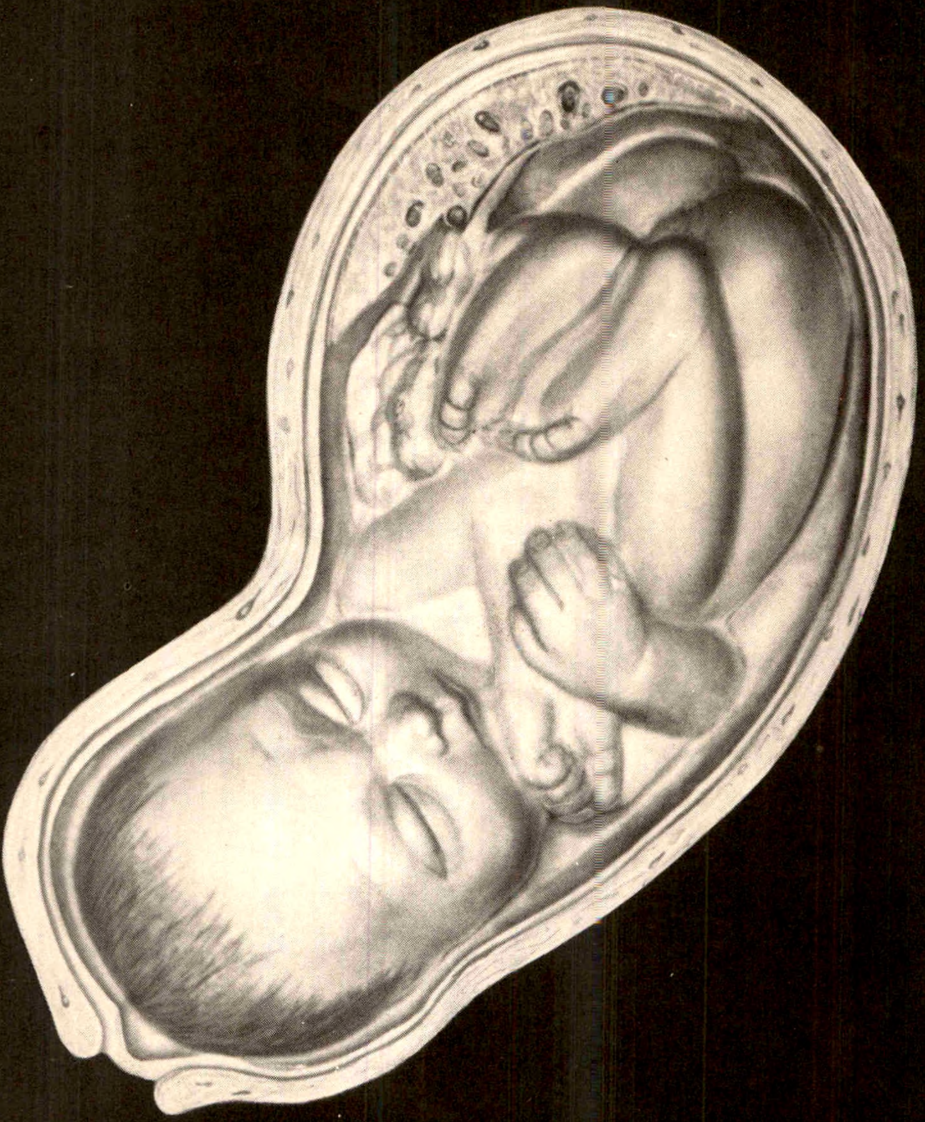
### FORMULA

| PRODUCT IDENTIFICATION | | | MULTIPLE DOSE VIAL | | | | | | SINGLE DOSE AMPUL | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marcaine HCl (brand of bupivacaine HCl) % | mg./ml. | Epinephrine* (as bitartrate) Dilution | Methylparaben mg./ml. | Sodium Bisulfite mg./ml. | Thioglycerol ml./ml. | Ascorbic Acid mg./ml. | 60% Sodium Lactate ml./ml. | Edetate Calcium Disodium mg./ml. | Sodium Bisulfite mg./ml. | Thioglycerol ml./ml. | Ascorbic Acid mg./ml. | 60% Sodium Lactate ml./ml. | Edetate Calcium Disodium mg./ml. |
| 0.25 | 2.5 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 0.25 | 2.5 | 1:200,000 | 1 | 0.5 | .001 | 2 | .0017 | 0.1 | .5 | .001 | 2 | .0017 | 0.1 |
| 0.5 | 5.0 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 0.5 | 5.0 | 1:200,000 | 1 | 0.5 | .001 | 2 | .0017 | 0.1 | .5 | .001 | 2 | .0017 | 0.1 |
| 0.75 | 7.5 | — | Not Available in Vials | | | | | | — | — | — | — | — |
| 0.75 | 7.5 | 1:200,000 | | | | | | | .5 | .001 | 2 | .0017 | 0.1 |

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved. Federal law prohibits dispensing without a prescription.

More protection
for the newborn



A drug of choice for epidural
anesthesia that results in

- decreased placental transfer[1]
- fewer neurobehavioral changes than lidocaine or mepivacaine[2,3]

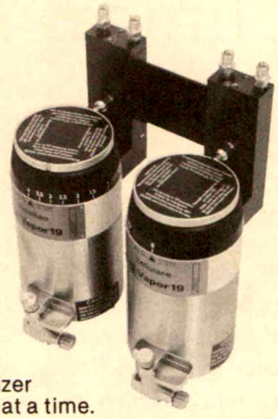
**Marcaine® hydrochloride**
brand of
**bupivacaine hydrochloride**
with or without epinephrine 1:200,000
See adjacent page for prescribing information. Not recommended for paracervical block.
Model © by Hubbard Scientific Co. Northbrook, Ill.

# NEW from NORTH AMERICAN DRÄGER

North American Drager is continually keeping in touch with the growing needs of the anesthesia profession. We are constantly improving our products for patient safety, our prime engineering and design criterion. These new products join the ever growing range of North American Drager Products of Anesthesia.

**DPM 2**
**(DRAGER PRESSURE MONITOR II)**

Our second generation of pressure monitors.
Four pressure monitors—minimum ventilation pressure, continuing pressure, high pressure and sub atmosphere pressure.

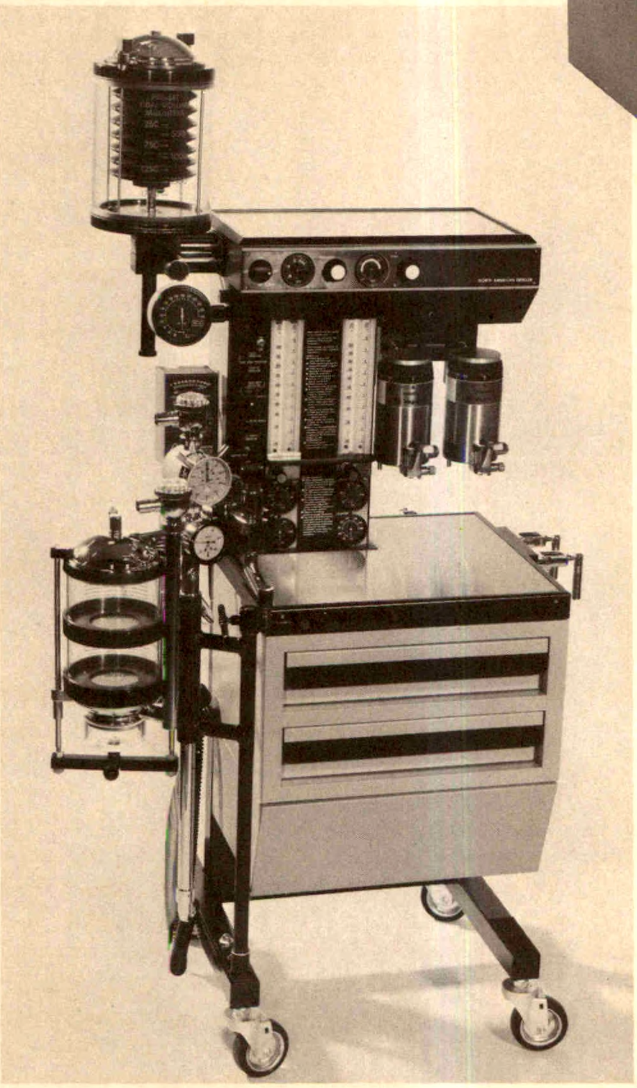


**VAPORIZER EXCLUSION SYSTEM**

A unique lock out system for insuring that only one vaporizer can be switched on at a time.

**PHILLIPS LARYNGOSCOPE BLADE**

Combines the features of the Miller Blade and the Jackson-Eversole Blade. Now in Two Sizes—Adult and Pediatric.



**NARKOMED 2 ANESTHESIA SYSTEM**

The newest member of the North American Drager family of Anesthesia Systems.
A complete anesthesia system consisting of an anesthesia dispensing system, ventilation system, patient monitoring system and a unique patient safety alarm system.

**NORTH AMERICAN DRÄGER**
148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969

**NORTH AMERICAN DRÄGER**
148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969

☐ Please send Anesthesia Accessories catalog

☐ Please have N.A.D. representative call

☐ Please include information on Anesthesia Machines

NAME ______________________
DEPARTMENT ______________________
HOSPITAL ______________________
ADDRESS ______________________
CITY ______________ STATE ____ ZIP ____
TELEPHONE ______________________

# EDITORIALS

# The Rate-Pressure Product in Clinical Anesthesia: Boon or Bane?

ANESTHESIOLOGISTS have unparalleled access to the cardiovascular system. Extensive hemodynamic evaluation can be made by using information obtained with intra-arterial and Swan-Ganz catheters.[1] However, despite this degree of sophistication, we still do not have a direct measurement of myocardial oxygen homeostasis. The development of therapeutic strategies to ensure a favorable balance between myocardial oxygen delivery and myocardial oxygen consumption is mandatory for patients with coronary artery disease undergoing anesthesia and surgery. In patients with restricted coronary blood flow, management should be directed at matching myocardial oxygen consumption to the limited oxygen supply. However, routine measurement of myocardial oxygen consumption ($M\dot{V}_{O_2}$) is not feasible for general clinical application. Therefore, the clinician must rely on various indirect indices of $M\dot{V}_{O_2}$ to aid in patient management.

Historically, several hemodynamic correlates have been proposed as indices of $M\dot{V}_{O_2}$. Myocardial oxygen consumption has been correlated with the products of: (1) heart rate and pulse pressure; (2) heart rate and mean aortic pressure; (3) systolic ejection period and the mean systolic pressure; and (4) heart rate and the peak systolic pressure.[2-5] The latter has been termed the rate-pressure product (RPP). Common to all these formulae is the use of a pressure measurement to estimate left ventricular (LV) wall tension (LV wall tension = LV radius × LV peak systolic pressure/wall thickness), a major determinant of $M\dot{V}_{O_2}$.

Investigators employing both direct and indirect methods for assessment of the heart's oxygen consumption have focused on six determinants of $M\dot{V}_{O_2}$. The Table lists the three major and three minor determinants and their relative contribution to $M\dot{V}_{O_2}$.[6,7] One should consider these factors carefully when extrapolating data in awake patients to the *supine* anesthetized patient. In exercise studies performed in the erect position, cardiac output and $M\dot{V}_{O_2}$ are increased by increasing stroke volume.[8] However, if exercise-induced stress is performed in the supine position, cardiac output is elevated mainly by an increase in heart rate rather than stroke volume. Further, changes in the contractile state of the heart, as seen with anesthetics, can greatly alter $M\dot{V}_{O_2}$ without changes in heart rate or blood pressure.[9] Based upon these complex interactions, how can we estimate changes in $M\dot{V}_{O_2}$ in the supine anesthetized patient?

In this issue Wilkinson and co-workers[10] have posed a significant clinical question: Is the rate-pressure product a valid hemodynamic correlate of $M\dot{V}_{O_2}$ in anesthetized patients? They have attempted to answer this question using an anesthetized canine model in which systemic arterial pressure was manipulated pharmacologically. $M\dot{V}_{O_2}$ was calculated by multiplying left anterior descending (LAD) coronary artery flow by the arterial-coronary sinus oxygen content difference. They report a good correlation ($r = 0.84$) between $M\dot{V}_{O_2}$ and the rate-pressure product in dogs anesthetized with a combination of halothane and morphine sulfate. However, these results must be interpreted with care due to methodologic limitations inherent in both the flow measurements and blood sampling techniques. LAD flow was used to estimate total coronary flow. The assumption is made that the portion of total coronary flow which traverses the LAD remains constant despite changing arterial pressure and heart rate. Furthermore, measuring coronary sinus oxygen content as a reflection of LAD venous drainage may introduce another source of error. The coronary sinus drains approximately 83% of the LV free wall and septum. However, the changes in blood pressure that occurred during the study could also alter the percentage of total LAD coronary flow which drains directly into the coronary sinus.[11,12] Despite

**TABLE**

**Determinants of Myocardial Oxygen Consumption ($M\dot{V}_{O_2}$)**

| Normally Beating Heart | Contribution to $M\dot{V}_{O_2}$ |
|---|---|
| | % |
| Major | |
| 1. Myocardial tension development | 30–40 |
| 2. Heart rate | —* |
| 3. Contractile state | 10–15 |
| Minor | |
| 4. External work | 10–15 |
| 5. Basal metabolism | 25 |
| 6. Electrical/chemical activity | <1 |

* Determines cumulative active energy expenditure per minute.

these considerations, it is interesting to note that the correlation coefficient between RPP and $M\dot{V}_{O_2}$ in the halothane-morphine anesthetized animals is similar to that reported for awake volunteers.[13] On the other hand, in halothane-anesthetized man, Sonntag and co-workers[14] recently reported a poor correlation between RPP and $M\dot{V}_{O_2}$.

Even if the rate-pressure product is accepted as an index of $M\dot{V}_{O_2}$ for the anesthetized patient, the clinical use of RPP is still beset with problems. In patients with cardiac disease undergoing anesthesia the absolute level of $M\dot{V}_{O_2}$ is not nearly so important as the balance between myocardial oxygen supply and demand. *Implicit* in the clinical application of RPP is a numerical value likely to be associated with myocardial ischemia. In critically examining the RPP as a possible index of myocardial oxygen balance, we must consider the differing effects of alterations in systolic blood pressure and pulse rate upon myocardial oxygenation. For example, an increase in systolic blood pressure may cause an increase in $M\dot{V}_{O_2}$. However, it may also concomitantly improve myocardial oxygenation by increasing coronary perfusion pressure. For a given patient, the predominant effect is difficult to predict a priori. In contrast, increasing heart rate is unlikely to improve myocardial oxygen balance since it presents a dual threat: increasing heart rate increases $M\dot{V}_{O_2}$ and magnifies the problem by decreasing diastolic duration, thereby impinging upon the time available for coronary perfusion. The effect of an increase in pulse rate upon the total diastolic time is striking. Recently Boudoulas et al[15] reported that an increase in heart rate from 50 to 75 beats per minute decreases total diastolic time by 50%. Not only is diastolic duration decreased but the relative duration of systole is increased.[16] Therefore, increasing heart rate simultaneously increases myocardial oxygen demand and decreases supply.

Anesthesiologists have attempted to establish maximum safe values for the RPP during anesthesia. An intraoperative study of anesthetized patients with coronary artery disease revealed that all patients whose RPP was greater than 12,000 developed ischemic electrocardiographic changes.[17] Subsequent to that report, a maximum RPP of 12,000 mm Hg × beats per minute has been often quoted as the level at which ischemia is likely to develop in patients with coronary artery disease. However, the authors emphasized that patients in the ischemic group had significantly higher heart rates than patients in the nonischemic group. This leaves us with the question: Did myocardial ischemia develop because the rate-pressure product was higher or because the pulse rate was significantly increased?

The rate-pressure product is indeed a product of two variables with differing effects. Thus, it is worthwhile to consider common values of pulse rate and systolic blood pressure and their effects upon RPP. For example, patient A with coronary artery disease can develop a RPP value of 12,000 if the heart rate (HR) is 75 beats per minute and the systolic arterial blood pressure (SBP) is 160 mm Hg. In this case the systolic arterial pressure (160) is likely to be associated with a high mean arterial perfusion pressure. The heart rate of 75 beats per minute allows approximately 410 msec for diastolic coronary flow. But a RPP of 12,000 in patient B can also result from a systolic blood pressure of 120 mm Hg and a heart rate of 100 beats per minute which allows only 280 msec for diastolic coronary flow. Do the numerically equal rate-pressure products represent equivalent clinical situations? Clearly not.

Similarly, does a decrease in RPP necessarily indicate improvement in myocardial oxygenation? Consider a patient with left main coronary artery disease who comes to the operating room with a RPP of 12,240 (HR = 90 beats per minute, SBP = 136 mm Hg). Following induction, systolic arterial pressure decreases to 80 mm Hg and the patient develops a tachycardia of 100 beats per minute. Now the RPP has decreased to 8,000. But, is myocardial oxygen balance really better?

Obviously, problems in interpretation of RPP exist and place limitations upon the measurement as an index of myocardial ischemia. As if this were not enough, technical considerations add further limitation. How should the arterial blood pressure measurements be made? Central systolic aortic pressure differs from radial artery pressure and both can differ from brachial artery pressure obtained by auscultation. Therefore, is a "cuff" RPP done preoperatively equivalent to an RPP calculated during anesthesia using a radial artery systolic pressure? Furthermore, direct arterial manometry from a radial artery can result in "systolic-overshoot" caused by resonance within the recording system. This overestimates the systolic arterial pressure and falsely elevates the RPP and can introduce yet another error.

As with many measurements in clinical medicine RPP has significant limitations. It may have a place in detecting trends in $\dot{M}V_{O_2}$ during anesthesia. But as Kissin et al[18] have also emphasized, RPP may be a *misleading* predictor of intraoperative myocardial ischemic injury. The clinician who uses the RPP must be continuously aware of these limitations and should always consider the separate effects of pulse rate and systolic arterial pressure upon myocardial oxygenation.

Paul G. Barash, MD
*Associate Professor of Anesthesiology*
Charles J. Kopriva, MD
*Associate Professor of Anesthesiology*
*Yale University School of Medicine*
*333 Cedar Street*
*New Haven, Connecticut 06510*

## REFERENCES

1. Barash P, Chen Y, Kitahata LM, et al: The hemodynamic tracking system: a method of data management and guide for cardiovascular therapy. Anesth Analg 59:169–174, 1980
2. Rhode E: Über den Einfluss der mechanischen Bedingungen auf die Tatigkeit und den Sauerstoffverbrauch des Warmbluterherzens. Arch Exp Pathol Pharmakol 68:401, 1912
3. Katz LN, Feinberg H: The relation of cardiac effort to myocardial oxygen consumption and coronary flow. Circ Res 6:656–669, 1958
4. Sarnoff S, Braunwald E, Welch GH Jr, et al: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. Am J Physiol 192:148–156, 1958
5. Cooper T Braunwald E, Morrow AG: Pulsus alternans in aortic stenosis. Circulation 18:64–70, 1958
6. Braunwald E: Control of myocardial oxygen consumption: physiologic and clinical considerations. Am J Cardiol 27:416–432, 1971
7. Gibbs CL Chapman JB: Cardiac energetics, in Handbook of Physiology: The Cardiovascular System. Section 2: The Heart, vol 1. Edited by RM Berne, N Sperelakis, SR Geiger. Washington, DC, American Physiological Society, 1979, pp 775–804
8. Braunwald E, Ross J Jr: Control of cardiac performance, in Handbook of Physiology, The Cardiovascular System. Section 2: The Heart, vol 1. Edited by RM Berne, N Sperelakis, SR Geiger. Washington, DC, American Physiological Society, 1979, pp 361–474
9. Sonnenblick EH, Ross J Jr, Covell JW, et al: Velocity of contraction as a determinant of myocardial oxygen consumption. Am J Physiol 209:919–927, 1965
10. Wilkinson PL, Tyberg JV, Moyers JR, et al: Correlates of myocardial oxygen consumption when after load changes during halothane anesthesia in dogs. Anesth Analg 59:233–239, 1980
11. Klocke F: Clinical measurements of coronary blood flow, in Progress in Cardiology. Edited by PN Yu, JF Goodwin. Philadelphia, Lea and Febiger, 1976, pp 91–130
12. Scharf SM, Bromberger-Barnea B, Permutt S: Distribution of coronary venous flow. J Appl Physiol 30:657–662, 1971
13. Kitamura K, Jorgensen CR, Gobel FL, et al: Hemodynamic correlates of myocardial oxygen consumption during upright exercise. Appl Physiol 32:516–522, 1972
14. Sonntag H, Merin RG, Donath U, et al: Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. Anesthesiology 51:204–210, 1979
15. Boudoulas H, Lewis RP, Rittgers SE, et al: Increased diastolic time: a possible important factor in the beneficial effect of propranolol in patients with coronary artery disease. J Cardiovasc Pharmacol 1:503–513, 1979
16. Greenspan K: Cardiac excitation, conduction and the electrocardiogram, in Physiology. Fourth edition. Edited by EE Selkurt, Boston, Little, Brown and Co, 1976, pp 311–359
17. Waller JL Kaplan JA, Jones EL: Anesthesia for coronary revascularization, in Clinical Cardiology Monographs. New York, Grune & Stratton, 1979, Chap 7, pp 260–261
18. Kissin I, Reves JG, Mardis S: RPP—A misleading guide? Anesthesiology, in press 1980

ANESTH ANALG
59:232, 1980

# Anesthesia Foundation Book Award

ON March 10, 1980, a singular event, the first of its kind in the annals of the history of anesthesia, took place in Reno, Nevada, during the 54th Congress of the International Anesthesia Research Society. On this date the Anesthesia Foundation made its previously announced award[1] for the the best book in anesthesiology published by an American author in the years 1978 and 1979. The award included a check for $5,000.

The anesthesia community owes a vote of thanks to the Anesthesia Foundation for its vision in making possible such a munificent award. The strength of any discipline can be judged by the quality of its publications. The richness and excellence of books published today by and for anesthesiologists deserve public recognition. What better way than public presentation of such a prestigious award?

The Anesthesia Foundation further deserves our congratulations for singling out for such distinction a clearly outstanding monograph written by a clearly deserving author. The recipient of the award was Dr. Raymond Fink, Professor of Anesthesiology at the University of Washington. The book which occasioned the award was his monograph, *Laryngeal Biomechanics*, co-authored by Robert Demarest, head of the Department of Medical Illustration at Columbia University, College of Physicians and Surgeons. Published by the Harvard University Press in 1978, the book is at once scholarly, thorough, innovative, beautifully written, and beautifully illustrated. *Laryngeal Biomechanics* represents the definitive exposition of the intracacies of how and why the larynx functions as it does. A seminal contribution, it has received well deserved kudos from anesthesiologists and nonanesthesiologists alike. As one reviewer, a particularly critical one, put it, the book "clarifies laryngeal biomechanics better than any other work available."[2] The book is also, as a not inconsiderable fringe benefit, a tribute to the art of medical publishing at its best. Few indeed are books in biomedical fields which are so tastefully and attractively designed and printed.

What makes the award even more appropriate is the recipient himself. *Laryngeal Biomechanics* represents the culmination of decades of study and research by Dr. Fink. Indeed, he has today become one of the world's authorities on the comparative and clinical anatomy and function of the larynx. This alone would amply justify such an award. But Dr. Fink's contributions to science in general and to anesthesia in particular have not been limited to the larynx. A Renaissance man in anesthesia if ever there was one, Dr. Fink's interests and contributions over the last 30 years have covered an astonishing array of diverse fields in anesthesia. Cellular biochemical responses to anesthetics, axonal transport mechanisms, teratogenicity of anesthetics, these are but some of the areas which have engaged Dr. Fink's attention. In each of them he has made equally outstanding contributions to our understanding of where, how, and why anesthetics act as they do. It is a pleasure indeed to see such an original thinker, such a perceptive student of anesthesia, receive an award so richly deserved.

Nicholas M. Greene, MD

## REFERENCES

1. Steinhaus JE: A milestone in anesthesiology: a book award (editorial). Anesth Analg 57:159, 1978
2. Kirchner JA: Laryngeal Biomechanics (book review). Anesthesiology 50:179, 1979

ANESTH ANALG
59:233-239, 1980

# Correlates of Myocardial Oxygen Consumption when Afterload Changes during Halothane Anesthesia in Dogs

**Philip L. Wilkinson, MB, BS,* John V. Tyberg, MD, PhD,† John R. Moyers, MD,* and Anne E. White, MS‡**

---

WILKINSON, P. L., TYBERG, J. V., MOYERS, J. R., AND WHITE, A. E.: Correlates of myocardial oxygen consumption when afterload changes during halothane anesthesia in dogs. Anesth Analg 59:233–239, 1980.

We have examined whether several clinically measurable correlates of myocardial oxygen consumption remain valid correlates when afterload changes during morphine or halothane plus morphine anesthesia. The correlates measured were heart rate, systolic blood pressure, left ventricular end diastolic pressure (LVEDP), and rate-pressure product (RPP). In six dogs we measured myocardial oxygen consumption (m$\dot{V}_{O_2}$) and hemodynamic variables during morphine (4 mg/kg) and during morphine-halothane (1.5% end tidal concentration) anesthesia. We changed ventricular afterload by infusion of nitroprusside or phenylephrine and measured m$\dot{V}_{O_2}$ as the product of left anterior descending coronary artery flow and arterial-coronary sinus oxygen content difference. RPP was the best correlate of m$\dot{V}_{O_2}$ during both morphine-halothane ($R = 0.84$) and morphine anesthesia ($R = 0.71$). Systolic pressure and LVEDP also significantly correlated with m$\dot{V}_{O_2}$ during both anesthetic states. The slope of the line relating RPP and m$\dot{V}_{O_2}$ was significantly ($p < 0.05$) depressed during added halothane anesthesia. This slope depression (0.016 vs 0.021) is of little practical consequence within the physiologic range of RPP. Regression analysis showed that systolic pressure and heart rate alone account for the major part of changes in m$\dot{V}_{O_2}$ during morphine-halothane anesthesia under the conditions of this experiment. After allowing for changes in LVEDP associated with systemic pressure, LVEDP still had significant effects on m$\dot{V}_{O_2}$ during morphine anesthesia, but not during morphine-halothane anesthesia. We conclude that RPP is the best correlate of m$\dot{V}_{O_2}$ under morphine-halothane anesthesia over a wide range of ventricular afterload states.

**Key Words:** ANESTHETICS, Volatile: halothane; ANESTHETICS, Intravenous: morphine; HEART: oxygen consumption.

---

ASSESSMENT of myocardial oxygen demand (m$\dot{V}_{O_2}$) during anesthesia and surgery is critical in patients with ischemic heart disease, cardiac failure, and anemia.

The major determinants of m$\dot{V}_{O_2}$ are ventricular wall tension, ventricular contractile performance, and heart rate[1] Of these determinants, contractile per-

---

* Assistant Professor, Anesthesia.

† Assistant Professor in Residence, Physiology, Medicine and Cardiovascular Research Institute.

‡ Staff Research Associate, Anesthesia.

Supported by Anesthesia Research Center Grant NIGMS GM15571-11, a grant from the Bay Area Heart Research Committee (P.L.W.), HL-06285 and a Grant in Aid (J.V.T.) from AHA with funds contributed in part by the California Affiliate.

Received from the Departments of Anesthesia, Medicine, and the Cardiovascular Research Institute, University of California Medical Center, San Francisco, California 94143. Accepted for publication September 18, 1979.

Reprint requests to Dr. Wilkinson, Department of Anesthesia, 436-S, University of California, San Francisco.

formance and wall tension are contributors of similar magnitude.[2] Wall tension is related to ventricular volume and intracavitary pressure by the law of Laplace; hence peak ventricular or peak systemic pressure correlate with wall tension in the absence of ventricular volume changes.

Although Rhode showed in 1912[3] that $m\dot{V}_{O_2}$ varied directly with the product of mean systolic pressure and heart rate, the product of heart rate and peak systolic pressure (RPP) has been most studied since that time. It is well correlated with $m\dot{V}_{O_2}$ in animals[4] and in awake, exercising man.[5] However, the relationship between RPP and $m\dot{V}_{O_2}$ during anesthesia has not been well described.

The hemodynamic effects of upright exercise in man are different from those seen during anesthesia. Exercise characteristically reduces ventricular volume,[6] slightly increases myocardial contractile performance, greatly increases heart rate, and slightly increases systolic blood pressure.[5] In contrast, halothane and other volatile anesthetic agents greatly decrease myocardial contractile performance,[7] increase ventricular volume,[8] decrease heart rate at any given blood pressure,[9] and decrease systolic blood pressure. Under these conditions, the relationship between RPP and $m\dot{V}_{O_2}$ may be altered, since RPP does not directly incorporate measurements of ventricular volume or contractile performance.

In an attempt to determine correlates of $m\dot{V}_{O_2}$ during anesthesia, we have examined the relationship between $m\dot{V}_{O_2}$ and several of its clinically measurable correlates in dogs during basal morphine anesthesia (4 mg/kg) and following the addition of halothane (1.5% end tidal concentrations). We changed $m\dot{V}_{O_2}$ by varying ventricular afterload during anesthetic states.

## Methods

In six mongrel dogs whose weights ranged between 22–32 kg we induced anesthesia with sodium thiopental (10 mg/kg IV) followed by morphine sulfate in 10-mg incremental doses to 4 mg/kg. At half-hour intervals we supplemented this dose with 0.1 mg/kg IV. We administered succinylcholine (2 mg/ml) by intravenous infusion throughout the experiment at a rate just sufficient to prevent spontaneous ventilation. An endotracheal tube was inserted and the animals were ventilated throughout the experiment using a Harvard animal respirator. Oxygen (100%) was administered except when halothane was added. Blood gas tensions were measured frequently and ventilation adjusted to maintain arterial $Pa_{CO_2}$ between 35 to 45 torr; $Pa_{O_2}$ was greater than 100 torr throughout the experiments. If a base deficit greater than 5 meq/L occurred we administered sodium bicarbonate until the deficit was less than 5.

The following instrumentation was used in all dogs. We attached standard electrocardiographic limb leads. Through a femoral artery cutdown we inserted a catheter and measured central aortic pressure (P23Db, Statham Instruments, Oxnard, CA). We measured left ventricular pressure using a catheter-tip transducer (Millar Instruments Inc, Houston, TX) inserted via a carotid artery cutdown. Through a left thoracotomy incision, we attached a calibrated flow probe (Carolina Medical Electronics, King, NC) around the proximal left anterior descending coronary artery. We inserted a catheter approximately 2.5 cm beyond the coronary sinus ostia and into the great cardiac vein. Data obtained throughout the experiment were photographically recorded (model 1858, Honeywell Inc, Denver, CO) at 100 mm/sec at selected times.

The catheter tip transducer was calibrated for gain against a mercury manometer in air before insertion and zero was adjusted after insertion so that measured pressure was the same as that obtained from another calibrated transducer attached to the reference lumen of the catheter. Zero coronary flow was calibrated by manual occlusion of the coronary artery immediately beyond the probe.

Following instrumentation, we induced changes in left ventricular afterload by nitroprusside infusion (0.1 mg/ml) and phenylephrine infusion (0.02 mg/ml). Systemic pressure was varied over a mean pressure range of 40–160 torr. The infusion rates were adjusted after each measurement to obtain a 20 torr change in systolic pressure. When the animals had remained hemodynamically stable for 5 minutes at a given pressure we recorded data and took aortic and coronary sinus blood samples to measure blood gas tensions and oxygen content. We repeated this sequence for five or six determinations over the full pressure range.

We randomly varied the sequence of halothane administration to minimize time-related hemodynamic changes. In three dogs we administered halothane in measured 1.5% end tidal concentration following anesthetic induction and morphine administration, and performed the protocol. In these three animals we then made measurements during morphine anesthesia after turning off the halothane and waiting until end tidal halothane concentrations were less than 0.05%. This waiting period was never less than 1 hour in duration. In the remaining dogs, we made measurements during morphine anesthesia first, and took halothane measurements after 1.5% end tidal concentrations were achieved and remained stable for 30 minutes.

End tidal gas samples for halothane determinations were obtained from an endotracheal catheter. Halothane concentrations were measured with a UV halothane meter (Cavitron) calibrated daily using a gas containing a known halothane concentration. Blood gas tensions were measured (Radiometer model BGM 2) and the instrument was calibrated before every measurement. Blood oxygen saturation and blood hemoglobin content were determined using a hemoximeter (Radiometer OSM2) calibrated daily; blood oxygen content was determined using a modified Klingenmeier method.[10]

We measured systolic arterial blood pressure, heart rate, left ventricular end diastolic pressure, the preejection period, left ventricular ejection time, left anterior descending coronary artery flow, and arterial and coronary sinus oxygen contents. The preejection period (PEP) was the average of six successive measured intervals from the beginning of the QRS complex to the beginning of systole on the central aortic pressure tracing. Left ventricular ejection time (LVET) was the similarly averaged duration of ejection measured from the central aortic tracing of the same beats.

The product of left anterior descending (LAD) coronary arterial flow and the aortic-coronary sinus oxygen content difference was used to represent $m\dot{V}_{O_2}$, thus assuming that coronary sinus oxygen content was representative of venous outflow from the region supplied by the LAD beyond the flow probe. Oxygen consumption measured in this manner is less than total $m\dot{V}_{O_2}$ since it neglects myocardium receiving right coronary and left circumflex coronary flow. However, this measured parameter is proportional to total $m\dot{V}_{O_2}$ in the absence of coronary vascular disease. In addition, the LAD coronary artery supplies a large portion of the left ventricle,[11] the ventricle of interest in the present study.

Statistical analysis of the derived data was conducted using heirarchical multiple regression.[12] In this form of regression one fits by linear least squares analysis a regression equation to the data, obtaining the equation constants, a multiple correlation coefficient (R), and a coefficient of determination ($R^2$). The latter is the proportion of total variance shared by the dependent variable ($m\dot{V}_{O_2}$) and the optimally weighted independent variables (systolic blood pressure, heart rate, left ventricular end diastolic pressure, and the ratio [PEP/LVET]). Optimal weights are determined by the least squares regression. This form of regression is done repeatedly using first one, then two, then three, then four independent variables and obtaining $R^2$ for each regression. The increase in $R^2$ that occurs when two variables are regressed instead of one indicates how much that second variable has added to the first in explaining the variance of $m\dot{V}_{O_2}$. Similarly, the addition of each successive variable may account for more variance, and the increase in $R^2$ that occurs is a measure of this. Using this form of analysis, one can estimate how $m\dot{V}_{O_2}$ correlates with systolic blood pressure, heart rate, left ventricular end diastolic pressure, and the PEP/LVET ratio, and describe the quantitative contribution of each under the conditions of the experiment.[12]

Heirarchical multiple regression was conducted using an Exidy microcomputer programmed for multiple regression in BASIC.[13]

## Results

Table 1 summarizes the univariate regressions and correlations between $m\dot{V}_{O_2}$ and measured parameters. Fig 1, upper left panel, shows the scattergram of data points relating systolic blood pressure and $m\dot{V}_{O_2}$. Although both halothane and morphine anesthetized animals show significant correlations between these variables, there is less scatter of data points during morphine-halothane anesthesia reflected by the greater value of r.

Fig 1, lower left panel, shows no significant univariate correlation between heart rate and $m\dot{V}_{O_2}$ during either morphine or morphine-halothane anesthesia. The variation in heart rate is greater during morphine (126 ± 42, mean ± SD, vs 109 ± 16, mean ± SD), and since both pressure and heart rate are determinants of $m\dot{V}_{O_2}$, this greater heart rate variation may have contributed to the increased scatter seen in the $m\dot{V}_{O_2}$-systolic pressure relationship during morphine anesthesia (Fig 1, upper left panel).

Combining heart rate and systolic blood pressure as the RPP yields a close relationship with $m\dot{V}_{O_2}$ (Fig 2). The correlation coefficients during both morphine and morphine-halothane anesthesia are highly significant ($p < 0.01$). The difference between regression slopes for morphine and morphine-halothane was tested for significance by F ratio calculation.[14] $p$ was 0.012 for this difference, indicating that the slope during morphine-halothane anesthesia is significantly less than during morphine anesthesia alone. While statistically significant, the difference is not great. For

**TABLE 1**

**Univariate Regressions (Six Dogs) and Correlations between Myocardial Oxygen Consumption and Variables of Interest***

| | Morphine | Halothane-morphine |
|---|---|---|
| $m\dot{V}_{O_2}$ vs systolic blood pressure | n = 28 | n = 43 |
| "r" | 0.41 | 0.79 |
| Y intercept | 227.6 | 58.9 |
| Slope | 0.68 | 0.152 |
| $m\dot{V}_{O_2}$ vs heart rate | | |
| "r" | 0.05 | 0.05 |
| Y intercept | 286.3 | 188.2 |
| Slope | 0.129 | 0.245 |
| $m\dot{V}_{O_2}$ vs left ventricular end diastolic pressure | | |
| "r" | 0.52 | 0.73 |
| Y intercept | 268.4 | 120.6 |
| Slope | 4.94 | 5.18 |
| $m\dot{V}_{O_2}$ vs PEP/LVET | | |
| "r" | −0.10 | 0.52 |
| Y intercept | 328.1 | 86.8 |
| Slope | −0.308 | 187.8 |
| $m\dot{V}_{O_2}$ vs rate pressure product | | |
| "r" | 0.71 | 0.84 |
| Y intercept | 8.2 | 42.1 |
| Slope | 0.016 | 0.021 |

* Abbreviations used are: $m\dot{V}_{O_2}$, myocardial oxygen consumption; PEP, preejection period; LVET, left ventricular ejection time.

example, an RPP of 16,000 is associated with an $m\dot{V}_{O_2}$ of 300 ml/min during morphine-halothane anesthesia and 345 ml/min during morphine anesthesia. The difference becomes negligible when RPP has normal values of 6,000 to 10,000 because the regression lines intersect in this range of values.

Fig 1, upper right panel, plots significant relationships between left ventricular end diastolic pressure (LVEDP) and $m\dot{V}_{O_2}$. There is less scatter during administration of halothane.

Fig 1, lower right panel, shows the lack of a significant relationship between the contractility ratio PEP/LVET[15] and $m\dot{V}_{O_2}$. However, halothane produced a small but statistically significant increase in the ratio (0.60 ± 0.21, morphine 0.65 ± 0.21, halothane, $p < 0.05$ by paired *t*-test.).

Table 2 summarizes the results of heirarchical multiple regression. This statistical technique was used to assess quantitatively the contribution of each variable to $m\dot{V}_{O_2}$. The coefficient of determination $R^2$ measures the amount of variation in $m\dot{V}_{O_2}$ that can be explained by the least squares regression equation for the variable(s) concerned. With morphine anesthesia, when systolic pressure and $m\dot{V}_{O_2}$ were regressed, $R^2 = 0.17$. This means that 17% of the variation in $m\dot{V}_{O_2}$ is associated with variation in systolic arterial pressure. When heart rate is added to the regression, $R^2 = 0.44$, and 44% of the variation in $m\dot{V}_{O_2}$ is explained by the combination of systolic pressure and heart rate. Since 17% was explained previously by systolic arterial

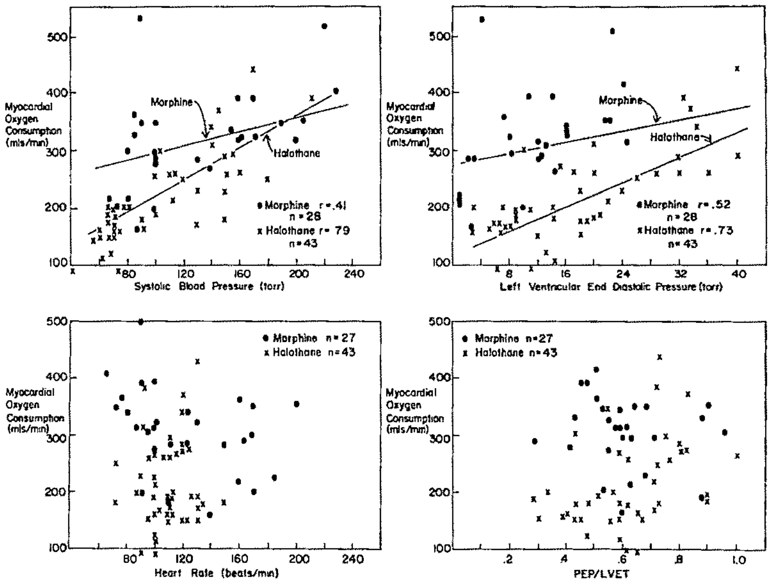


FIG 1. Correlates of myocardial oxygen consumption: Upper left panel, significant relationship between $m\dot{V}_{O_2}$ and systolic blood pressure during both morphine and added halothane anesthesia; upper right panel, similar relationships between $m\dot{V}_{O_2}$ and LVEDP; lower two panels show no significant relationship between $m\dot{V}_{O_2}$ and heart rate, or between $m\dot{V}_{O_2}$ and the contractility index PEP/LVET.

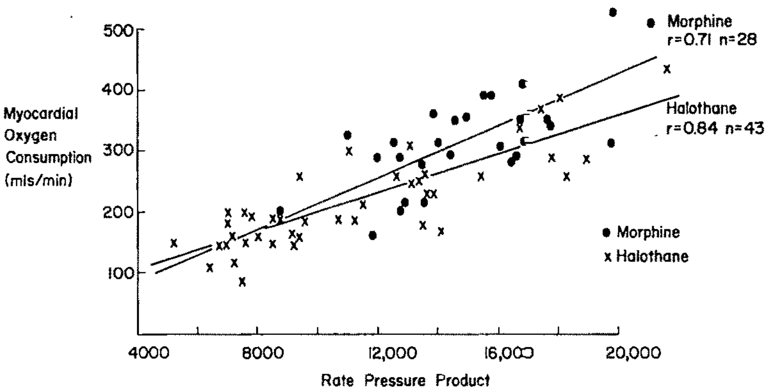


FIG 2. Rate pressure product correlates with $m\dot{V}_{O_2}$ during both morphine and added halothane anesthesia over a wide range of rate pressure product and a 5-fold increase in $m\dot{V}_{O_2}$.

**TABLE 2**

**Multiple Regressions***

| Anesthetic agents | Regression equation | Multiple correlation coefficient (R) | Coefficient of determination ($R^2$) | Increase in $R^2$ from previous value ($\Delta R^2$) | Significance (*p* value) of $\Delta R^2$ |
|---|---|---|---|---|---|
| Morphine | $m\dot{V}_{O_2}$ = 227.6 + 0.68 SBP | 0.41 | 0.17 | 0.17 | 0.029 |
| | $m\dot{V}_{O_2}$ = 1.68 SBP + 1.1 HR − 21.0 | 0.66 | 0.44 | 0.27 | 0.0019 |
| | $m\dot{V}_{O_2}$ = 1.60 SBP + 2.0 HR + 4.4 LVEDP-101.3 | 0.74 | 0.55 | 0.11 | 0.023 |
| | $m\dot{V}_{O_2}$ = 1.69 SBP + 1.82 HR + 3.2 LVEDP-93.9 PEP/LVET-108.5 | 0.76 | 0.58 | 0.03 | 0.21 |
| Morphine-halothane | $m\dot{V}_{O_2}$ = 58.9 + 1.52 SBP | 0.79 | 0.63 | 0.63 | <0.0001 |
| | $m\dot{V}_{O_2}$ = 1.655 SBP + 1.3 HR-98.4 | 0.83 | 0.70 | 0.07 | 0.004 |
| | $m\dot{V}_{O_2}$ = 1.31 SBP + 1.11 HR + 1.47 LVEDP-67 | 0.84 | 0.71 | 0.01 | 0.25 |
| | $m\dot{V}_{O_2}$ = 1.37 SBP + 1.06 HR + 1.48 LVEDP-21.9 PEP/LVET-53.6 | 0.84 | 0.71 | 0 | — |

* Summary of multiple regression statistics, showing regression equations multiple correlation coefficients, and coefficient of determination $R^2$. $\Delta R^2$ is the increase in $R^2$ occurring from the previous regression correlation, and is the proportion of variance accounted for by the additional variable added to the regression, e.g., ventricular end diastolic pressure in the third equation, morphine section, accounts for 11% of the variance ($\Delta R^2 = 0.11$) in myocardial oxygen consumption when added to heart rate and systolic pressure, which together previously accounted for 44% ($R^2 = 0.44$) of the variance in myocardial oxygen consumption. *p* values are the probability that the associated $\Delta R^2$ occurred by chance alone. $m\dot{V}_{O_2}$, myocardial oxygen consumption; SBP, systolic arterial blood pressure; HR, heart rate; LVEDP, left ventricular end diastolic pressure; PEP, preejection period; LVET, left ventricular ejection time.

pressure, heart rate has independently contributed 44 − 17 or 27%. The significance of the contribution of each variable can be assessed[12] and is expressed as the *p* value in the table. Hence during morphine anesthesia, systolic arterial pressure (17%), heart rate (27%), and LVEDP (11%) made significant contributions to the determination of $m\dot{V}_{O_2}$. When halothane was added, only systolic blood pressure (63%) and heart rate (7%) made significant contributions to the determination of $m\dot{V}_{O_2}$.

## Discussion

Under the conditions of this experiment, RPP has the highest correlation with $m\dot{V}_{O_2}$ of the variables measured or calculated. The correlation is enhanced when halothane is added to basal morphine anesthesia. Also when systolic pressure and heart rate are combined as a multiple linear regression equation there are similar high correlations with $m\dot{V}_{O_2}$ during both anesthetics (Table 2).

The degree of correlation of $m\dot{V}_{O_2}$ with its three major determinants (ventricular wall tension, contractile performance, and heart rate) depends on the conditions under which the correlation is measured. Only an index that incorporates all of the determinants of $m\dot{V}_{O_2}$ will correlate well independently of the circumstances of the experiment. Single variables such as heart rate or blood pressure will correlate highly with $m\dot{V}_{O_2}$ if the experimental conditions produce changes in $m\dot{V}_{O_2}$ mainly via changes in that variable. Hence during exercise, where major heart rate changes occur, heart rate itself correlates almost as well as RPP.[5] Conversely, because the tension time index does not directly contain a measure of contractility, it is an insensitive correlate of $m\dot{V}_{O_2}$ when $m\dot{V}_{O_2}$ is changed mainly by altering contractile performance with isoproterenol.[1]

The relationship between $m\dot{V}_{O_2}$ and heart rate, contractility, and systolic arterial blood pressure is different during exercise than during halothane anesthesia. Halothane anesthesia and surgery are associated with decreased contractility, decreased systolic blood pressure, and little change in heart rate,[7-9] whereas exercise greatly increases rate and slightly increases contractility and systolic blood pressure.

With these considerations in mind, we chose to vary $m\dot{V}_{O_2}$ in a way that has clinical relevance but does not greatly disturb what we considered the primary effect of halothane—depression of contractile performance. Decreasing peripheral vascular resistance and left ventricular afterload with nitroprusside has the clinical counterpart of hypotensive anesthesia using nitroprusside in conjunction with halothane. Similarly, phenylephrine-induced increases in peripheral vascular resistance and left ventricular afterload have the clinical counterpart of phenylephrine infusion to maintain cerebral perfusion during carotid endarterectomies, and resemble the effects of aortic cross-clamping during halothane anesthesia for vascular surgical procedures.

Because we chose primarily to vary systolic arterial blood pressure and hence ventricular wall tension in this manner, it is not surprising that systolic pressure makes the largest contribution to $m\dot{V}_{O_2}$ during halothane anesthesia. Compared to the awake state, responses of heart rate to changing pressure are decreased.[9] During morphine anesthesia, when baroreflexes are not depressed, heart rate varies over a wider range and makes a greater contribution to $m\dot{V}_{O_2}$ (27% vs 7%). Heart rate when considered alone is not significantly correlated with $m\dot{V}_{O_2}$ (Fig 1, lower left panel), perhaps because in our model, heart rate changes are secondary to blood pressure changes. Multiple regression unmasks the contribution of heart rate to $m\dot{V}_{O_2}$ after allowing for concurrent changes in systolic pressure which may have obscured the relationship in Fig 1, lower left panel.

Although significant univariate correlations exist between $m\dot{V}_{O_2}$ and LVEDP during both morphine halothane ($r = 0.73$) and morphine anesthesia ($r = 0.52$), multiple regression analysis suggests that this correlation is the result of the correlation between LVEDP and systolic blood pressure ($r = 0.91$ for morphine, $r = 0.83$ for halothane). After multiple regression of systolic pressure and heart rate, the variance in $m\dot{V}_{O_2}$ explainable by any independent effect of LVEDP is much reduced.

Changes in LVEDP, while making a significant (11%) contribution to $m\dot{V}_{O_2}$ during morphine anesthesia are insignificant (1%) during morphine-halothane anesthesia (Table 2). Perhaps during morphine anesthesia the greater heart rate changes seen may have influenced LVEDP independently of afterload, by altering diastolic filling time.

The index PEP/LVET has been used to assess myocardial contractility noninvasively.[15] Halothane significantly, but only slightly, increased the mean values of this index, indicating depressed contractility. No significant correlation exists with $m\dot{V}_{O_2}$, perhaps because of the small change and because the experimental model did not produce large additional changes in contractile performance independent of anesthetic effects as afterload changed.

The RPP has long been used as a correlate of $m\dot{V}_{O_2}$.[3-5] Our study confirms the validity of this relationship during both morphine and halothane-morphine anesthesia. The slope of the relationship is significantly less during the administration of halothane, perhaps reflecting a decreased contractile state and less oxygen consumption. The absolute value of this slope difference does not result in large differences in $m\dot{V}_{O_2}$ at any given RPP during morphine or halothane anesthesia except at large values of RPP (Fig 2).

In conclusion, $m\dot{V}_{O_2}$ correlates with RPP under the hemodynamic conditions of this experiment. Although the slope of the relationship is decreased during halothane-morphine anesthesia, this appears of little practical significance. Insofar as our results can be extrapolated to man, they indicate the RPP is a valid correlate of $m\dot{V}_{O_2}$ under halothane-morphine anesthesia, despite gross changes in ventricular afterload as might be seen during hypotensive anesthesia and aortic cross-clamping. The results do not indicate the validity or otherwise of the relationship when $m\dot{V}_{O_2}$ is changed by other factors, such as increased contractile performance, heart rate, and systolic blood pressure due to autonomic stimulation during "light" anesthesia. However, the hemodynamic changes of "light" anesthesia more closely resemble those seen during exercise, when RPP is a good correlate of $m\dot{V}_{O_2}$.[5]

## REFERENCES

1. Braunwald E: Control of myocardial oxygen consumption: physiologic and clinical considerations. Am J Cardiol 27:416–432, 1971
2. Graham TP Jr, Covell JW, Sonnenblick EH, et al: Control of myocardial oxygen consumption: relative influence of contractile state and tension development. J Clin Invest 47:375–385, 1968
3. Rhode E: Über den Einfluss des mechanischen Bedingungen und die Tetigkeit and den Sauerstoffverbrauch des Warmbluterhergens. Arch Exp Pathol Pharmacol 68:401, 1912
4. Antic R, Hirsch LJ, Katz LH: The factors controlling myocardial oxygen consumption per stroke and per minute. Acta Cardiol 20:309–321, 1965
5. Kitamura K, Jorgensen CR, Gobel FL, et al: Hemodynamic correlates of myocardial oxygen consumption during upright exercise. J Appl Physiol 32:516–522, 1972
6. Bevegard BS, Shepherd JT: Regulation of the circulation during exercise in man. Physiol Rev 47:178–213, 1967
7. Goldberg AH, Alrich WC: Effects of halothane on isometric contractions of isolated heart muscle. Anesthesiology 28:838–845, 1967
8. Hamilton WK, Larson CP, Bristow JD, et al: Effect of cyclopropane and halothane on ventricular mechanics; a change in ventricular diastolic pressure-volume relationships. J Pharmacol Exp Ther 154:566–574, 1966
9. Duke PC, Fownes D, Wade JG: Halothane depresses baroreflex control of heart rate in man. Anesthesiology 46:184–187, 1977
10. Duke GE, Newhouse YMG: Micromethod for measuring blood oxygen content by determining oxygen tension after saturation with carbon monoxide. Am Rev Respir Dis 110:814–816, 1974
11. James TN: Anatomy of the Coronary Arteries. New York, Hoeber & Co, 1961, p 173
12. Cohen J, Cohen P: Applied Multiple Regression Correlation Analysis for the Behavioral Sciences. John Wiley and Sons, New York, 1975, pp 98–102
13. Poole L, Borches M: Some Common BASIC Programs, 2nd Edition. Berkeley, CA, Adam Osborne and Assoc Inc, 1978, pp 147–150
14. Zar JH: Biostatistical Analysis. Englewood Cliffs, NJ, Prentice-Hall, 1974, pp 228–235
15. Garrard CL, Weissler AM, Dodge HT: The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. Circulation 42:455–462, 1970

ANESTH ANALG
59:240-244, 1980

# Myocardial Function during Halothane and Enflurane Anesthesia in Patients with Coronary Artery Disease

**Thomas J. Delaney, MD,* James R. Kistner, MD,† Carol L. Lake, MD,† and Edward D. Miller, Jr., MD‡**

---

DELANEY, T. J., KISTNER, J. R., LAKE, C. L., AND MILLER, E. D., JR.: Myocardial function during halothane and enflurane anesthesia in patients with coronary artery disease. Anesth Analg 59: 240–244, 1980.

Halothane and enflurane are known myocardial depressants in healthy individuals. Whether these two agents produce the same degree of myocardial depression in patients with coronary artery disease has not been studied. Informed consent was obtained from 16 adults with ischemic heart disease undergoing coronary artery bypass grafting. Patients with significant ventricular dysfunction were excluded from the study. Control measurements were made while the patient breathed 100% oxygen. The patients were divided into two groups, anesthetized with either halothane or enflurane, and repeat measurements made at ½ and ¾ MAC for each agent. The last series of measurements (¾ MAC) was made approximately 1 hour after the induction of anesthesia but before intubation, surgical skin preparation or surgical incision. Our data indicate that at ½ and ¾ MAC for halothane, mean arterial blood pressure (MAP) decreased from 92 ± 2 torr to 73 ± 3 torr and 67 ± 2 torr, respectively ($p < 0.05$). Pulmonary capillary wedge pressure (PCWP) increased from 6.2 ± 0.7 torr to 9.1 ± 1.6 torr and 9.4 ± 1.7 torr at ½ and ¾ MAC halothane ($p < 0.05$). Cardiac index decreased from the control values of 2.67 ± 0.08 L/min/m$^2$ to 2.19 ± 0.06 L/min/m$^2$ for ½ MAC and to 2.24 ± 0.08 L/min/m$^2$ at ¾ MAC halothane ($p < 0.05$). Assisted ventilation was maintained throughout and arterial $P_{CO_2}$ was unchanged from control. Enflurane likewise resulted in a decrease in MAP from 99 ± 6 torr to 75 ± 4 torr at ½ MAC and 68 ± 5 torr at ¾ MAC ($p < 0.05$). PCWP did not increase. In contrast, however, cardiac index was unchanged from control value of 2.65 ± 0.16 L/min/m$^2$ at both ½ and ¾ MAC. Arterial $P_{CO_2}$ was unchanged from the awake control value. Our data indicate that while both halothane and enflurane decrease mean arterial blood pressure, the mechanisms responsible differ. The primary afterload-reducing effect of enflurane may be beneficial to some patients with ischemic heart disease whereas other patients may benefit from the greater myocardial depression seen with halothane.

**Key Words:** ANESTHETICS, Volatile: halothane; ANESTHETICS, Volatile: enflurane; HEART: myocardial function; ANESTHESIA: cardiovascular.

---

HALOTHANE has been repeatedly shown to be a myocardial depressant in a variety of species, including healthy human volunteers.[1-4] Studies of enflurane, on the other hand, have produced variable

---

* Fellow.

† Assistant Professor.

‡ Associate Professor.

Supported in part by Research Career Development Award #1 K04 GMoo457-01 from the National Institutes of Health (E.D.M.).

Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication November 20, 1979. Presented in part at the 54th Congress of the International Anesthesia Research Society, Reno, Nevada, March 1980.

Reprint requests to Dr. Miller.

results. Although several investigators[4-7] have found enflurane to be either more depressant or equally depressant to the myocardium as compared to equipotent concentrations of halothane, others[8-10] have found halothane to be more depressant than enflurane.

Halothane and enflurane are both used extensively in cardiac surgical patients. No study has compared the cardiovascular effects of these agents in patients with coronary artery disease. One cannot necessarily extrapolate from healthy, normal individuals to these patients.[11] We therefore compared the hemodynamic effects of these agents at equipotent concentrations after induction of anesthesia but before the start of surgery in patients undergoing coronary revascularization procedures.

## Methods

Informed consent was obtained from 16 adults (14 men, 2 women) with ischemic heart disease undergoing coronary artery bypass grafting; they were alternately placed into two groups. Patients with significant ventricular dysfunction as judged by cardiac catheterization findings (i.e., ejection fraction <50%) or left ventricular end-diastolic pressure (LVEDP) >15 torr were excluded from the study. Clinical factors (i.e., age, LVEDP, height, weight, history of myocardial infarction, chronic or preoperative digitalization, daily propranolol dosage, and the number of vein grafts to be performed) were recorded.

Patients were premedicated with morphine, 0.1 mg/kg, and scopolamine, 0.3 to 0.4 mg, 1 hour before being brought to the operating room where two large peripheral venous cannulae were inserted, a radial artery was percutaneously cannulated, and a #7 thermodilution pulmonary artery catheter was placed by a modified Seldinger technique via the right internal jugular vein. Electrocardiogram (ECG), electroencephalogram, radial and pulmonary arterial pressures, pulmonary capillary wedge pressures (PCWP) and central venous pressure (CVP) were recorded on an 8-channel Hewlett-Packard recorder. Bentley Trantec transducers, calibrated daily against mercury, were used.

ABBREVIATIONS

| | |
|---|---|
| CI | cardiac index (L/min/m$^2$) |
| CO | cardiac output (L/min) |
| CVP | central venous pressure (torr) |
| HR | heart rate (beats/min) |
| LVEDP | left ventricular end-diastolic pressure (torr) |
| LVSWI | left ventricular stroke work index (g-m/m$^2$) |
| MAP | mean arterial pressure (torr) |
| $M\dot{V}O_2$ | myocardial oxygen consumption |
| PCWP | pulmonary capillary wedge pressure (torr) |
| RPP | rate pressure product (beats/min-torr) |
| SVI | stroke volume index (ml/beat/m$^2$) |
| SVR | systemic vascular resistance (dynes/sec/cm$^5$) |

After the patient breathed 100% oxygen by mask for 5 minutes, cardiac output, heart rate, ECG, arterial and pulmonary artery pressures, PCWP, CVP, and arterial blood gases were measured and recorded. Minute ventilation was also noted during this awake period. Following these baseline measurements, anesthesia was induced with either halothane (group 1) or enflurane (group 2) in 100% oxygen by mask (5 to 6 L of fresh gas flow). The end-tidal anesthetic concentration sampled from the mask was measured continuously with a Beckman LB-II infrared analyzer. After an end-tidal concentration of ½ MAC had been reached (requiring 20 to 30 minutes), it was maintained constant for 10 minutes, at which time the previous measurements were repeated. None of the patients studied, experienced an overt excitement phase. The end-tidal concentration was then increased to ¾ MAC and after 10 minutes of equilibration the measurements were repeated. During the induction, ventilation was assisted gently by hand to maintain minute ventilation at approximately the control level.

Cardiac output was measured in duplicate by thermodilution using an Edwards model 9510A cardiac output computer and temperature curves were recorded to observe for artifacts. ST-depression was measured in the $V_5$ lead of a calibrated ECG tracing. The rate pressure product (RPP) as well as indices derived from standard equations[12] including cardiac index (CI), systemic vascular resistance (SVR), stroke volume (SV), stroke volume index (SVI), and left ventricular stroke work index (LVSWI) were calculated at a later time from the recording. RPP is the product of systolic arterial pressure and heart rate.

The Beckman LB-II analyzer was calibrated to known concentrations of anesthetic as measured by gas chromatography. Standard MAC values for healthy middle-aged adults (1.68% for enflurane,[13] 0.77% for halothane[14]) were used in calculating the ½ MAC and ¾ MAC concentrations. Statistical analysis was performed using Student's t-test for paired and unpaired data. Differences were considered statistically significant if $p < 0.05$. Values are presented as means ± standard error of the mean (SEM).

This study was approved by the University of Virginia Medical Center Human Investigation Committee. All studies were performed before surgical skin preparation, endotracheal intubation, or surgical incision. Esophageal temperature taken shortly after the end of the study period ranged from 35.5–37 C.

## Results

Both groups were similar in age, height, weight, body surface area, ventricular function, number of vein grafts, and mean daily propranolol dosage (average 35 mg q.i.d.). Five of eight patients given halothane and three of eight patients given enflurane had histories of previous myocardial infarctions. One patient in each group was receiving long-term digitalis therapy; the remainder were digitalized preoperatively (1.0 mg over 24 hours) as is the practice at this institution. No patient had symptoms or signs of significant congestive heart failure. The two women were both given enflurane. There was no ECG evidence of worsening ischemia in either group during the study. All patients were clinically asleep (as evidenced by failure to respond to a verbal command) at both the ½ MAC and ¾ MAC levels.

### Group I-Halothane

In the patients anesthetized with halothane there were significant decreases at both anesthetic concentrations in MAP, CO, CI, SVI, HR, LVSWI, SVR, and RPP (except for SVI at ¾ MAC, which was unchanged). Significant increases were noted in PCWP and CVP (Table 1). There were no significant changes from control in $P_{O_2}$, $P_{CO_2}$, or pH (Table 2).

### Group II-Enflurane

In patients anesthetized with enflurane there were significant decreases in MAP, SVR, LVSWI, and RPP at both anesthetic concentrations. There was no significant change in CO, CI, SVI, HR, PCWP, or CVP. There was an increase in $P_{O_2}$ at the ½ MAC level; however, $P_{CO_2}$ and pH were unchanged (Table 1).

### Halothane versus Enflurane

Comparison of halothane and enflurane revealed that MAP fell to similar levels (67 torr and 68 torr, respectively at ¾ MAC) and the heart rates were similar (52 and 55, respectively) with both anesthetics; however, CI was significantly higher with enflurane at both ½ MAC and ¾ MAC (2.80 and 2.91 L/min/m$^2$, respectively) than with halothane (2.19 and 2.24 L/min/m$^2$, respectively). In addition, SVI was higher with enflurane at both levels and CO was higher with enflurane at ½ MAC. There were no significant differences in PCWP, CVP, SVR, LVSWI, or arterial blood gas tensions (Table 1).

**TABLE 1**

**Hemodynamic Measurements during Halothane and Enflurane Anesthesia**

| | Halothane | | | Enflurane | | |
|---|---|---|---|---|---|---|
| | Control | ½ MAC | ¾ MAC | Control | ½ MAC | ¾ MAC |
| CO (L/min) | 5.21 ± 0.28 | 4.24 ± 0.14* | 4.35 ± 0.23* | 4.90 ± 0.24 | 5.22 ± 0.40† | 5.42 ± 0.50 |
| CI (L/min/m$^2$) | 2.67 ± 0.08 | 2.19 ± 0.06* | 2.24 ± 0.08* | 2.65 ± 0.16 | 2.80 ± 0.17† | 2.91 ± 0.23† |
| MAP (torr) | 92 ± 2 | 73 ± 3* | 67 ± 2* | 99 ± 6 | 75 ± 4* | 68 ± 5* |
| HR (beats/min) | 57 ± 4 | 53 ± 3* | 52 ± 3* | 53 ± 3 | 54 ± 3 | 55 ± 3 |
| PCWP (torr) | 6.25 ± 0.70 | 9.13 ± 1.57* | 9.38 ± 1.65* | 8.75 ± 1.46 | 8.75 ± 1.06 | 8.38 ± 1.27 |
| CVP (torr) | 3.50 ± 0.42 | 6.25 ± 1.03* | 6.75 ± 1.27* | 3.88 ± 1.11 | 6.13 ± 1.19 | 5.63 ± 0.94 |
| SVR (dynes/sec/cm$^5$) | 1396 ± 99 | 1264 ± 71* | 1118 ± 77* | 1572 ± 131 | 1093 ± 104* | 973 ± 133* |
| SVI (ml/beat/m$^2$) | 48 ± 3 | 42 ± 2* | 44 ± 3 | 51 ± 3 | 52 ± 3† | 53 ± 3† |
| RPP (beats/min-torr) | 7961 ± 622 | 5631 ± 352* | 5056 ± 348* | 8022 ± 676 | 5847 ± 486* | 6010 ± 716 |
| LVSWI (g-m/m$^2$) | 59 ± 3 | 39 ± 4* | 37 ± 4* | 66 ± 6 | 50 ± 3* | 46 ± 5* |

* $p < 0.05$ compared to control.

† $p < 0.05$ compared to halothane at corresponding level.

**TABLE 2**

**Arterial Blood Gas Analysis during Halothane and Enflurane Anesthesia**

| | Halothane | | | Enflurane | | |
|---|---|---|---|---|---|---|
| | Control | ½ MAC | ¾ MAC | Control | ½ MAC | ¾ MAC |
| $P_{O_2}$ (torr) | 357 ± 20 | 376 ± 22 | 386 ± 28 | 366 ± 17 | 396 ± 16* | 380 ± 17 |
| $P_{CO_2}$ (torr) | 42 ± 1 | 44 ± 1 | 45 ± 2 | 43 ± 1 | 43 ± 1 | 43 ± 1 |
| pH | 7.39 ± 0.01 | 7.36 ± 0.01 | 7.34 ± 0.01 | 7.37 ± 0.01 | 7.37 ± 0.01 | 7.37 ± 0.01 |

* $p < 0.05$ compared to control.

## Discussion

Halothane is a well known myocardial depressant and has been shown to decrease all the standard indices of myocardial function.[1, 4, 7, 14] The decrease in contractility results in a dose-related decrease in cardiac output which is due to a decrease in stroke volume rather than to a decreased heart rate.[14] Systemic vascular resistance is usually minimally decreased[15] or unchanged.[3]

The effects of enflurane on cardiovascular dynamics remain somewhat controversial. In vitro studies[2, 7, 10] have demonstrated a negative inotropic effect of enflurane on isolated cat heart papillary muscles. Laboratory studies involving intact dogs[6] and rhesus monkeys[4] demonstrated that enflurane depresses left ventricular function in a dose-related manner equal to or greater than that produced by halothane. However, studies in humans have shown a variety of results. Levesque et al[16] demonstrated in normal volunteers that enflurane (average 2.29% end-tidal concentration) significantly decreased mean arterial pressure and total peripheral resistance, with no change in cardiac output. Comparing enflurane and halothane, both Kaplan et al[9] using systolic time intervals, and Rathod et al[8] using echocardiography, found halothane to be more depressant to the myocardium than enflurane. Conversely, Smith et al[5] demonstrated that, in healthy volunteers, enflurane causes a marked dose-related decrease in both cardiac output and total peripheral resistance, and increase in heart rate.

Both halothane and enflurane are commonly used in patients with coronary artery disease, both for cardiac and noncardiac surgery. The hemodynamic effects of anesthetics may be different in patients with coronary artery disease and healthy volunteers.[11] Our data indicate that at relatively low concentrations both anesthetics cause a marked decrease in mean arterial pressure; however, the mechanism is different with each. Halothane decreases both cardiac output and systemic vascular resistance, while enflurane decreases systemic vascular resistance alone. Furthermore, halothane causes an increase in both PCWP and CVP which was not seen with enflurane, again suggesting greater myocardial depression with halothane than with enflurane. These findings suggest that in patients with coronary artery disease, who are digitalized and taking propranolol preoperatively, enflurane does not result in impairment of left ventricular function. However, left ventricular function is not synonymous with cardiac output. The decrease in afterload probably resulted in a shift of the Starling plot to the left, i.e., cardiac output does not depend exclusively on contractility. We suspect that the decrease in afterload masked a certain amount of myocardial depression by enflurane.

When anesthetizing patients with coronary artery disease for cardiac or noncardiac surgery a major consideration is prevention of increases in myocardial oxygen demand, since oxygen supply remains relatively fixed. The major determinants of oxygen demand are left ventricular wall tension (a function of volume related to both preload and afterload), the contractile state, and heart rate.[17] As both anesthetics reduced MAP, with no change in HR and little change in PCWP it is likely that myocardial oxygen consumption ($M\dot{V}_{O_2}$) was reduced. Reduction of $M\dot{V}_{O_2}$ with halothane and enflurane has been demonstrated experimentally.[6, 18] However, it would appear from our data that the effects on the determinants of oxygen demand may be different with the two anesthetics in patients with coronary artery disease. Halothane decreases the contractile state, heart rate, and afterload and so presumably decreases $M\dot{V}_{O_2}$ while slightly increasing preload; on the other hand enflurane reduces afterload only.

Since no ischemic ECG changes were seen in either group and the differences in other indices of myocardial demand were not marked, we cannot state that either anesthetic agent resulted in more favorable myocardial oxygenation. We might hypothesize that in low doses, enflurane may be preferable to halothane in patients with borderline ventricular function because of the reduction in afterload associated with enflurane. This however requires further study.

At first appearance, the low concentrations of anesthetic agents studied, may seem too low for meaningful clinical interpretation. However, these relatively low end-tidal concentrations were chosen because in pilot studies 1 MAC anesthesia resulted in marked hypotension. Kaplan et al[19] found that in healthy volunteers 0.87% mixed expired halothane resulted in a mean arterial pressure of only 49 torr. In our study without surgical stimulation, ½ or ¾ MAC halothane resulted in a MAP of 73 ± 3 torr and 67 ± 2 torr, respectively, while ½ or ¾ MAC enflurane resulted in a MAP of 75 ± 4 torr and 68 ± 5 torr, respectively. To counteract the profound hypotensive properties of both of these agents, the addition of narcotics, nitrous oxide, and muscle relaxants is common practice so that decreased concentrations of inhalational agents are necessary. Furthermore, the discrepancy between the inspired concentration and the actual end-tidal concentration is rarely appreciated in clinical practice. It should be noted that at the termination of the study, the patients received a muscle relaxant, were intubated, and 50% nitrous oxide administered. The end-tidal concentration of the inhalational agent was rarely increased. These patients appeared anesthetized as evidenced by loss of consciousness, loss of lid reflex, anmesia, and a blunted blood pressure response to intubation and surgical incision.

In summary, our data indicate that in patients with coronary artery disease and good ventricular function, the cardiovascular effects of halothane and enflurane are quantitatively different.

## REFERENCES

1. Merin RG, Kumazawa T, Luka NL: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. Anesthesiology 44:402-415, 1976
2. Shimosato S, Augai N, Swatsuki N, et al: The effect of Ethrane on cardiac muscle mechanics. Anesthesiology 30:513-518, 1969
3. Eger EI, Smith NT, Stoelting RK, et al: Cardiovascular effects of halothane in man. Anesthesiology 32:396-409, 1970
4. Ritzman RJ, Erickson HH, Miller ED: Cardiovascular effects of enflurane and halothane on the rhesus monkey. Anesth Analg 55:85-91, 1976
5. Smith NT, Calverley RK, Prys-Roberts C, et al: Impact of nitrous oxide on the circulation during enflurane anesthesia in man. Anesthesiology 48:345-349, 1978
6. Merin RG, Kumazawa T, Luka NL: Enflurane depresses myocardial function, perfusion, and metabolism in the dog. Anesthesiology 45:501-507, 1976
7. Brown BR, Crout JR: A comparative study of the effects of five general anesthetics on myocardial contractility. Anesthesiology 34:236-245, 1971
8. Rathod R, Jacobs HK, Kramer NE, et al: Echocardiographic assessment of ventricular performance following induction with two anesthetics. Anesthesiology 49:86-90, 1978
9. Kaplan JA, Miller ED, Bailey DR: A comparative study of enflurane and halothane using systolic time intervals. Anesth Analg 55:263-268, 1976
10. Kemmotsu O, Hashimoto Y, Shimosato S: The effects of fluroxene and enflurane on contractile performance of isolated papillary muscles from failing hearts. Anesthesiology 40:252-260, 1974
11. Stoelting RK, Creasser CW, Gibbs PS, et al: Circulatory effects of halothane added to morphine anesthesia in patients with coronary artery disease. Anesth Analg 53:449-455, 1974
12. Grossman W: Cardiac Catheterization and Angiography. Philadelphia, Lea and Febiger, 1974
13. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. Anesthesiology 35:361-364, 1971
14. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. Anesthesiology 30: 488-491, 1969
15. Bahlman SH, Eger EI, Halsey MJ, et al: The cardiovascular effects of halothane in man during spontaneous ventilation. Anesthesiology 36:494-502, 1972
16. Levesque PR, Nanagas V, Shanks C, et al: Circulatory effects of enflurane in normocarbic human volunteers. Can Anesth Soc J 21:580-585, 1974
17. Braunwald E: Control of myocardial oxygen consumption: physiologic and clinical considerations. Am J Cardiol 27:416-432, 1971
18. Bland JH, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287-293, 1976
19. Kaplan JA, Bush GL, Lecky JH, et al: Sodium bicarbonate and systemic hemodynamics in volunteers anesthetized with halothane. Anesthesiology 42:550-558, 1975

ANESTH ANALG
59:245-249, 1980

# Psychological Functioning after Halothane or Enflurane Anesthesia

**Lowell H. Storms, PhD,* Andrew H. Stark, BS †**
**Roderick K. Calverley, MD,‡ and N. Ty Smith, MD§**

---

STORMS, L. H., STARK, A. H., CALVERLEY, R. K., AND SMITH, N. T.: Psychological functioning after halothane or enflurane anesthesia. Anesth Analg 59:245–249, 1980.

Halothane and enflurane anesthesia were administered without surgery to young volunteer subjects who were compared with unanesthetized control subjects. All subjects were tested for intellectual function, visual-motor coordination, and personality characteristics, and they were asked to complete a symptom checklist on three occasions: before anesthesia, 2 days after anesthesia, and 2 weeks after anesthesia. Except for slight temporary effects in a few individuals, anesthesia altered neither intellectual or visual-motor measures nor personality characteristics. Although both anesthetics induced a number of symptoms persisting for 2 days after anesthesia, malaise was clearly greater following halothane than enflurane. Halothane was specifically associated with difficulty in remembering things, difficulty in concentrating, faintness or dizziness, and having to do things slowly to do them right. These symptoms were absent at the 2-week test.

**Key Words:** ANESTHETICS, Volatile: halothane; ANESTHETICS, Volatile: enflurane; PSYCHOLOGIC RESPONSES: postoperative.

---

THE USE of enflurane has dramatically increased since its introduction into clinical practice in 1971. In large part, this widespread acceptance has resulted from enflurane's low biodegradation and organ toxicity. Although hepatotoxicity appears to be minimal or absent with this agent, a concern remains over the effects of enflurane on the central nervous system.

Enflurane anesthesia may induce seizure activity particularly at deeper levels and/or if accompanied by hypocapnia.[1] The potential for this cerebral effect to result in brain changes which persist at least transiently following anesthesia is suggested by reports from two groups of investigators: (1) Julien and Kaven[2] reported on cats with indwelling electrodes that were given 4.5 to 5.5% enflurane in 44% oxygen and showed high frequency, high voltage spiking, EEG activity for 2 to 14 days following anesthesia. (2) Ohm et al[3] reported case histories of two patients who experienced grand mal seizures several days following enflurane anesthesia. Both patients recovered without apparent sequelae and no other such cases have been published.

Other studies have given inconclusive or negative evidence of significant postanesthetic central nervous system effects of enflurane. Wollman et al,[4] for example, demonstrated that convulsive activity during enflurane anesthesia was not associated with abnormalities in jugular venous $P_{O_2}$ or cerebral metabolic

---

* Professor, Department of Psychiatry, University of California, San Diego, and Staff Psychologist, San Diego VA Medical Center.

† Department of Psychology, University of Hawaii, Honolulu, Hawaii.

‡ Associate Clinical Professor of Anesthesia, University of California, San Diego, and Staff Anesthesiologist, San Diego VA Medical Center.

§ Professor, Department of Anesthesia, University of California, San Diego, and Staff Anesthesiologist, San Diego, VA Medical Center.

Supported in part by the Medical Research Service of the Veterans Administration, by National Institutes of Health grant GMS-15771, and by a grant from Ohio Medical Products.

Received from the San Diego Veterans Administration Medical Center, 3350 La Jolla Village Drive, San Diego, California 92161. Accepted for publication December 13, 1979. Presented at the 1976 Annual Meeting of the American Society of Anesthesiologists.

Reprint requests to Dr. Storms, Psychology Service, 116B, San Diego Veterans Administration Medical Center.

rate.[4] In 12 volunteers who were anesthetized with enflurane for 9.6 MAC-hours, Burchiel et al[5] found no postanesthetic EEG spiking or convulsive activity. Half of these volunteers experienced grand mal seizures during anesthesia and all displayed spiking activity. In a paper¶ presented at the 1975 Annual Meeting of the American Society of Anesthesiologists Steinhelber indicated that transient impairment of mental function could occur in older (more than 53 years) patients given enflurane for 2 to 3 hours. Three but not 6 days after anesthesia, the patients anesthetized with enflurane scored lower than halothane anesthetized patients on several tests of intellectual function. On the other hand, patients given halothane reported more symptoms, suggesting a residual source of depression or discomfort.

In contrast to the interest in residual cerebral effects following enflurane anesthesia, little concern has been expressed regarding possible postanesthetic effects of halothane. Yet there is evidence that postanesthetic effects do exist. Davison et al[6] found mental and symptomatic abnormalities for 2 to 4 days following anesthesia in volunteers given halothane. These abnormalities often were greater than those seen following administration of isoflurane, an isomer of enflurane. EEG spiking activity has been seen after halothane anesthesia but not after enflurane anesthesia. Three of seven volunteers showed "sharp" waves following 13 to 14 MAC-hours of halothane.[7]

Given the uncertainty regarding the postanesthetic mental effects of enflurane and halothane, we measured intellectual and symptomatic changes following administration of these anesthetics to volunteers. Volunteers were examined because, unlike patients, they could be subjected to a long, reasonably standardized anesthetic experience without superimposition of the potentially confounding effects of surgery. We hypothesized that either anesthetic would produce measurable deficits 2 days after anesthesia which would disappear within 2 weeks following anesthesia.

## Methods

Twenty-seven male volunteers willing to undergo general anesthesia for pay were recruited from local college campuses. Subjects who received enflurane anesthesia and control subjects came from one campus and subjects who received halothane anesthesia came from another. There were no significant differences among the three groups in age, Wechsler Adult Intelligence Scale (WAIS) Verbal, Performance, or Full Scale IQs, or Minnesota Multiphasic Personality Inventory (MMPI) Scales (Table 1). Volunteers from the same campus (control volunteers and those given enflurane) were randomly assigned to their respective groups.

Three categories of psychological tests were used: Intelligence, personality, and cerebral dysfunction. Intelligence was assessed with the 11 subtests of the WAIS (first items on Table 1). Personality tests included the MMPI and a symptom checklist. Tests of cerebral dysfunction included the Bender Visual-Motor Gestalt, the Grassi Block Substitution Test, and the Graham-Kendall Memory for Designs.[8, 9] All are standard tests except for the symptom checklist which was used in the studies of Davison et al[6] and Steinhelber.¶

The entire battery of psychological tests was administered to all subjects on three occasions. For subjects who were anesthetized, the tests were administered prior to anesthesia, 2 days after anesthesia, and 14 to 16 days after anesthesia. Control subjects, not given anesthesia, were tested at comparable intervals. All volunteers underwent a rigorous medical evaluation prior to admission to the study, including a complete medical history, physical examination, and appropriate laboratory tests to assure that each was in excellent health. Subjects selected for anesthetic underwent arterial and central venous cannulation under local anesthesia while resting on an ultra-low-frequency air-bearing hallistocardiograph bed. Control measurements were taken with the subjects awake before the induction of anesthesia by mask. Details of the anesthetic protocol are presented elsewhere.[10, 11] The average halothane anesthesia lasted 13.7 ± 0.8 SEM MAC-hours compared with 9.6 ± 0.9 SEM MAC-hours of enflurane anesthesia. Both groups were anesthetized for nearly the same amount of time, but subjects receiving halothane could tolerate higher concentrations of anesthetic.

The results were analyzed using analyses of variance which compared the two anesthesia groups with each other and with the control groups across three occasions (a mixed design with repeated measures).

These studies were approved by the Human Research Committees of the University of California, San Diego, and the Veterans Administration Medical Center, San Diego. A detailed consent was obtained from all subjects.

---

¶ Steinhelber J, Eger EI II, Durandetto BE, et al: Psychological effects of halothane and enflurane anesthesia in older patients. Abstracts of Scientific Papers, 1975 Annual Meeting of the American Society of Anesthesiologists, pp 231–232.

TABLE 1

Mean Test Scores before Anesthesia Baseline and Mean Changes in Scores ($\Delta\bar{X}$) ± Standard Error of the Mean (SEM) two Days and two Weeks after Anesthesia

| | Pre-anesthesia baseline | | | 2 days after anesthesia minus preanesthesia $\Delta\bar{X}_1 \pm SEM_1$ | | | 2 weeks after anesthesia minus preanesthesia $\Delta\bar{X}_2 \pm SEM_2$ | | | (df = 2, 50) F* |
|---|---|---|---|---|---|---|---|---|---|---|
| | Halothane | Enflurane | Control | Halothane | Enflurane | Control | Halothane | Enflurane | Control | |
| WAIS Information | 13.14 | 12.42 | 12.67 | .00 ± .44 | .42 ± .72 | .44 ± .38 | .43 ± .37 | .75 ± .37 | .89 ± .42 | 3.07 *† |
| Comprehension | 14.00 | 11.42 | 11.44 | −.14 ± .86 | −.25 ± .57 | .56 ± .38 | 1.71 ± 1.01 | .33 ± .62 | 1.44 ± .71 | 4.26 *† |
| Arithmetic | 13.00 | 10.00 | 12.11 | .57 ± .37 | 1.25 ± .46 | .57 ± .63 | .29 ± .36 | 2.00 ± .41 | 1.33 ± .44 | 12.15 § |
| Similarities | 13.43 | 11.00 | 13.00 | .00 ± .62 | .42 ± .75 | .59 ± .42 | .43 ± .53 | 1.42 ± .67 | 1.33 ± .17 | 5.46 *‡ |
| Vocabulary | 13.86 | 12.67 | 12.89 | −.29 ± .29 | .17 ± .30 | .11 ± .26 | .57 ± .57 | .50 ± .38 | .00 ± .53 | 1.34 NS |
| Digit Symbol | 12.29 | 10.92 | 12.11 | .29 ± .42 | −.08 ± .48 | 1.22 ± .70 | 2.00 ± .69 | 1.67 ± .40 | 1.22 ± 1.05 | 8.47 § |
| Picture Completion | 11.57 | 12.50 | 12.78 | 1.14 ± .55 | .58 ± .48 | .57 ± .58 | 1.00 ± .62 | .92 ± .63 | .67 ± .76 | 4.07 † |
| Block Design | 12.71 | 12.33 | 12.44 | .43 ± .57 | 1.42 ± .50 | 1.22 ± .36 | 1.00 ± .38 | 2.67 ± .62 | 1.89 ± .56 | 14.99 § |
| Picture Arrangement | 12.71 | 11.50 | 10.67 | .86 ± .71 | 1.42 ± .50 | 2.56 ± .88 | 1.71 ± 1.76 | 1.25 ± .82 | 3.78 ± 1.15 | 7.39 ‡ |
| Object Assembly | 11.14 | 12.08 | 12.33 | 1.71 ± 1.32 | .83 ± 1.13 | 2.89 ± .68 | 3.00 ± .90 | 3.17 ± 1.18 | 3.89 ± .84 | 17.28 § |
| Digit Span-Forward | 6.50 | 7.14 | 7.44 | −.29 ± .36 | .50 ± .40 | .00 ± .24 | .71 ± .18 | .92 ± .34 | .11 ± .20 | 3.50 † |
| Digit Span-Backward | 5.86 | 4.83 | 6.33 | .29 ± .52 | .67 ± .43 | −.11 ± .39 | .00 ± .54 | 1.33 ± .38 | .00 ± .29 | 1.50 NS |
| WAIS Verbal IQ | 119.57 | 109.08 | 114.88 | .57 ± .90 | 3.42 ± .97 | 2.89 ± 1.54 | 3.86 ± 1.57 | 6.75 ± 1.51 | 7.00 ± 1.58 | 23.99 § |
| Performance IQ | 113.43 | 111.08 | 113.44 | 5.29 ± 3.21 | 7.17 ± 1.76 | 11.22 ± 2.41 | 11.86 ± 3.71 | 14.75 ± 3.31 | 15.22 ± 2.38 | 36.70 § |
| Full Scale IQ | 117.71 | 110.58 | 115.11 | 2.86 ± 1.87 | 4.58 ± .98 | 6.89 ± 1.69 | 7.86 ± 2.10 | 10.00 ± 2.50 | 11.11 ± 1.79 | 32.95 § |
| Bender-Gestalt (Hain Score) | 1.86 | 2.28 | 2.11 | 1.00 ± .95 | −.09 ± .98 | −.56 ± .67 | 1.00 ± 1.07 | −.18 ± 1.23 | −.79 ± .66 | .01 NS |
| Graham-Kendall (Raw Score) | .57 | .37 | .62 | .29 ± .47 | .91 ± .64 | −.22 ± .46 | −.57 ± .57 | −.18 ± .23 | −.56 ± .34 | 2.98 NS |
| Graham-Kendall (Difference Score) | .29 | −1.18 | −.62 | .29 ± .47 | 1.09 ± .73 | −.33 ± .55 | −.29 ± .29 | .18 ± .23 | .00 ± .60 | .69 NS |
| Total Symptoms | 2.28 | 8.92 | 7.41 | 22.14 ± 6.00 | 10.86 ± 4.01 | −3.89 ± 1.58 | 3.14 ± 3.30 | −1.86 ± 1.24 | −3.56 ± 1.20 | None |

* Analysis of variance of practice effects across occasions. (There were no differences between groups except on symptoms.)

† $p < 0.05$.

‡ $p < 0.01$.

§ $p < 0.001$.

## Results

Intellectual assessment with the WAIS yielded the expected practice effects. The IQ score often increased 10 points or more on successive testing (Table 1). No significant intellectual deficits in either group could be attributed to the anesthetics. Similarly, none of the three neuropsychological tests revealed any differences between groups ( $p > 0.50$ in each case), including any differences due to anesthesia. Thus, neither halothane nor enflurane gave any evidence of postanesthetic cortical dysfunction. These results are summarized in Table 1.

However, both anesthetics produced a few idiosyncratic findings. One subject given enflurane suffered a temporary impairment on the Memory for Designs Test 2 days after anesthesia. Interestingly, he also had difficulty with short-term auditory memory for digits prior to anesthesia and 2 days afterward, but not 2 weeks later. Another volunteer given enflurane displayed perseveration on the Bender Gestalt test, increased anxiety on the MMPI, and some decrements on three WAIS subtests 2 days after anesthesia, but not 2 weeks later. Two subjects given halothane showed slight decreases in auditory memory for digits 2 days but not 14 days after anesthesia, and one subject showed slight temporary changes on the Bender Gestalt. No problems were observed in the control group.

Both halothane and enflurane produced physical discomfort as defined by the symptom checklist. Within 2 weeks virtually all of the symptoms had abated (Table 2). Both anesthetics produced effects suggestive of depression: low energy, poor appetite, and trouble falling or staying asleep. However, neither anesthetic significantly affected the MMPI Depression Scale.

**TABLE 2**

**Symptoms Associated with Anesthesia Administration* Two Days after Anesthesia**

*Symptoms associated equally with both halothane and enflurane*

- Number of symptoms reported
- Low in energy
- Weakness in parts of the body
- Nausea from motion
- Poor appetite
- Muscle soreness
- Heavy arms and legs
- Difficulty falling or staying asleep
- Poor coordination
- Sweating
- Trembling
- Hot and cold spells
- Numbness or tingling
- Sore throat
- Dry mouth
- Smell of anesthesia

*Symptoms associated with both but more marked with halothane*

- (Number of symptoms reported)
- (Low in energy)
- (Weakness in parts of the body)
- (Nausea from motion)
- (Poor appetite)
- Faintness or dizziness
- Having to do things slowly to do them right

*Symptoms associated only with halothane*

- Trouble remembering things
- Trouble concentrating
- (Daytime drowsiness)
- (Coughing)
- (Hypochondriasis)

*Symptoms associated only with enflurane*

- (Headaches)

* All symptoms listed showed groups × time interaction in the appropriate analysis of variance which was statistically significant with $p < 0.05$, except that symptoms in parentheses had $p < 0.10$.

Some symptoms were more marked after halothane than after enflurane although associated with both anesthetics. Especially notable after halothane were faintness or dizziness and having to do things slowly to do them right. Of low statistical significance ( $p < 0.1$) but consistent with Steinhelber's report¶ were reduced energy, weakness, nausea, and poor appetite. Subjects given halothane, but not those given enflurane, reported more difficulty remembering things and difficulty concentrating. Only one symptom, headaches, seemed associated solely with enflurane ( $p < 0.1$).

Interestingly, the MMPI overcontrolled hostility scores for both experimental and control subjects increased 2 days after anesthesia and remained significantly higher at 2 weeks. This may reflect irritation with repeated testing.

## Discussion

Our results should be reassuring to those concerned about the potential of enflurane or halothane for the production of significant postanesthetic impairment of mental function. Neither the exposure to nor the dose of either anesthetic far exceeded that experienced by the ordinary patient. The subjects anesthetized with enflurane were those studied by Burchiel et al[5] and, as noted above, all had displayed high voltage spiking activity during anesthesia and half had had overt grand mal seizures. The subjects anesthetized with halothane also had been studied by Burchiel et al[7] and, as noted, had displayed postanesthetic EEG "sharp wave" activity. Alpha rhythm in the EEGs of subjects given either halothane or enflurane had decreased slightly 2 days but not 6 days following anesthesia.[7] Despite these stresses, neither halothane nor enflurane produced measurable postanesthetic deficits in intelligence in our subjects.

Our results slightly conflict with the results reported by both Steinhelber and by Davison et al.[6] In the Steinhelber study,¶ 3 days after anesthesia subjects who had been given enflurane scored lower than did subjects given halothane on the Wechsler Memory Scale and on two measures from the Neurological Index of Mental Impairment. These measures were not used in the present study because we preferred better standardized measures (measures with published validation and cross-validation studies). However, none of the intellectual or perceptual-motor measures in the current study, including measures of immediate memory, showed impairment following either anesthetic. A few subjects in both groups showed slight deficits 2 days after anesthesia which may or may not reflect mild temporary central nervous system dysfunction. It may be that our subjects recovered their mental faculties more rapidly because they were younger (Steinhelber's subjects were at least 55 years old) and had not undergone surgery.

The differences between our results and those produced by Davison et al cannot be explained by differences in age or the stress of surgery. As in our study, Davison used young healthy volunteers. The difference between our results and Davison's may be more apparent than real, since only a few of Davison's results demonstrated differences between anesthetized and control groups. Where Davison's study did show differences, several surprisingly favored the anesthetized group (for example, the Neurological Index of Mental Impairment tests for Similarities and Differences, for Arithmetic, and for Numerical Total). Such findings are what might be anticipated to develop randomly from the large number of variables examined. The few positive findings might similarly represent chance occurrences.

The symptom checklist appears to be a sensitive indicator of physical malaise. Our results from the symptom checklist agree with those from the previous studies that used this instrument. Although abbreviated exposures to enflurane and halothane for outpatient surgery have not demonstrated significant differences in postoperative complaints,[12] both in our study and the study presented by Steinhelber,¶ halothane caused more adverse symptoms than enflurane. Similarly, Davison et al found that halothane caused more adverse symptoms than isoflurane. These differences may have resulted from the lower solubility of enflurane and isoflurane relative to halothane and hence the slower elimination of halothane.[13] Alternatively, the metabolism of halothane to bromide may have produced blood levels sufficient to cause central nervous system effects.[14] Either of these or some unknown mechanism may account for the greater number of adverse symptoms after halothane than after enflurane.

In summary, except for minor transitory effects on a few scattered subjects, neither halothane nor enflurane had negative effects on intellectual or perceptual-motor functions in healthy young adult men. However, both anesthetics produced a number of symptoms that were evident 2 days after anesthesia but not 2 weeks later. Halothane produced more adverse symptoms than enflurane.

## REFERENCES

1. Neigh JL, Garman JK, Harp JR: The electroencephalographic pattern during anesthesia with Ethrane: effects of depth of anesthesia, $Pa_{CO_2}$ and nitrous oxide. Anesthesiology 35:482–487, 1971
2. Julien RM, Kavan EM: Electrographic studies of a new volatile anesthetic agent: enflurane (Ethrane). J Pharmacol Exp Ther 183:393–403, 1972
3. Ohm WW, Cullen BF, Amory DW, et al: Delayed seizure activity following enflurane anesthesia. Anesthesiology 42:367–368, 1975
4. Wollman H, Smith AL, Hoffman JC: Cerebral blood flow and oxygen consumption in man during electroencephalographic seizure patterns induced by anesthesia with Ethrane. Fed Proc 28:356, 1969
5. Burchiel KJ, Stockard JJ, Calverley RK, et al: Relationship of pre- and post-anesthetic EEG abnormalities to enflurane-induced seizure activity. Anesth Analg 47:509–514, 1977
6. Davison LA, Steinhelber JC, Eger EI II, et al: Psychological effects of halothane and isoflurane anesthesia. Anesthesiology 43:313–324, 1975
7. Burchiel KJ, Stockard JJ, Calverley RK, et al: Electroencephalographic abnormalities following halothane anesthesia. Anesth Analg 57:244–251, 1978
8. Graham FK, Kendall BS: Memory for designs test: revised general manual. Percept Mot Skills 11:147–183, 1960
9. Hirt M: An evaluation of the Grassi test for organic involvement. J Clin Psychol 14:48–50, 1958
10. Calverley RK, Smith NT, Jones CW, et al: Ventilatory and cardiovascular effects of enflurane anesthesia in man. Anesth Analg 57:610–618, 1978
11. Calverley RK, Smith NT, Prys-Roberts C, et al: Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 57:619–628, 1978
12. Kreinbuhl G: Subjektive Beschwerden nach Halothane und nach Enfluraneanaesthesie bei Ambulanten (Tagesklinik-) Patienten. Anaesthesist 27:533–537, 1978
13. Eger EI II: Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, chap 4
14. Mazze RI, Calverley RK, Smith NT: Inorganic fluoride nephrotoxicity, prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46:265–271, 1977

ANESTH ANALG
59:250-256, 1980

# A Halothane-Induced Biochemical Defect in Muscle of Normal and Malignant Hyperthermia-Susceptible Landrace Pigs

**G. Mitchell, BSc, BVSc, PhD,* J. J. A. Heffron, BSc, PhD,† and A. J. J. van Rensburg, MSc‡**

---

MITCHELL, G., HEFFRON, J. J. A., AND VAN RENSBURG, A. J. J.: A halothane-induced biochemical defect in muscle of normal and malignant hyperthermia-susceptible Landrace pigs. Anesth Analg 59:250–256, 1980.

Muscle adenosine triphosphate (ATP), glucose-6-phosphate, phosphocreatine, and pH were measured in nine malignant hyperthermia (MH)-susceptible and 14 MH-resistant Landrace pigs. Muscle biopsies were taken before (under barbiturate anesthesia) and after exposure to halothane. When compared to levels during barbiturate anesthesia, exposure to halothane had no immediate effect on muscle ATP levels in either MH-susceptible or -resistant pigs. However, once malignant hyperthermia developed in susceptible pigs ATP levels decreased significantly. In both susceptible and resistant pigs halothane increased muscle glucose-6-phosphate and decreased muscle phosphocreatine and pH significantly below control levels observed during barbiturate anesthesia. In susceptible pigs these changes were significantly more marked than were the changes produced in resistant pigs. These data indicate that the effect of halothane on muscle metabolism is similar in both MH-resistant and -susceptible pigs. The results suggest that the effect of halothane is to inhibit aerobic metabolism by preventing mitochondrial dehydrogenation of pyruvate. Inhibition is complete in susceptible pigs but only retarded in resistant pigs. In susceptible pigs the consequent lactacidosis, hyperthermia, and reduction in ATP synthesis contribute to the development and maintenance of rigidity.

**Key Words:** HYPERTHERMIA, Malignant; MUSCLE, Skeletal: metabolism; ANESTHETICS, Volatile: halothane.

---

IN SPITE of extensive research into the causes of stress susceptibility and malignant hyperthermia in pigs, the site of the underlying lesion or lesions remains obscure. Several hypotheses have been suggested. The classic explanation offered by Britt and Kalow[1] is that the sarcoplasmic reticulum (SR) cannot maintain normal resting calcium concentrations. The resulting high myoplasmic calcium inhibits troponin, activates myosin adenosine triphosphatase (ATPase) and phosphorylase, and uncouples oxidative phosphorylation, thus producing rigidity and hyperthermia. However, attempts to reverse the established syndrome using drugs that reestablish normal SR calcium concentrations have largely met with failure,[2-5] which suggests that the SR is not involved at a primary level. On the other hand drugs that in-

---

* Senior Lecturer, Department of Physiology, University of the Witwatersrand.

† Senior Lecturer, Department of Physiological Chemistry, University of the Witwatersrand. Present address: Department of Biochemistry, University of Cork, Cork, Ireland.

‡ Senior Professional Officer, Animal and Dairy Science Research Institute, Irene, South Africa.

This work was supported by the University of the Witwatersrand Council Research Committee.

Received from the University of the Witwatersrand, Medical School, Hospital Street, Johannesburg, South Africa. Accepted for publication December 16, 1979.

Reprint requests to Dr. Mitchell, Department of Physiology, School of Veterinary Science, Park Row, Bristol BS1 5LS, England.

creased myoplasmic calcium worsen the prognosis of malignant hyperthermia (MH) reactions.[6]

It has also been suggested that catecholamine release[7] and an uncoupling of oxidative phosphorylation[8] by halothane are the primary events, while loss of magnesium ions from the myoplasm has also been accorded a central role.[9] However, while these changes undoubtedly contribute to the development and maintenance of the syndrome, none satisfactorily explains all the clinical and biochemical changes that occur.

An explanation that would account for most of the changes that occur is that provided by Eikelenboom and van den Bergh[10] who have shown that mitochondria prepared from stress-susceptible pigs have a significantly lower rate of oxygen consumption than mitochondria prepared from normal pigs. In the study of Eikelenboom and van den Bergh[10] synthesis of ATP in mitochondria of stress-susceptible pigs was, consequently, low when nicotinamide adenine dinucleotide (NAD)-linked substrates (L-glutamate and L-malate) were used. If this were found to be so in vivo, then reduced mitochondrial synthesis of ATP would lead to increased glycolysis and inactivation of the SR calcium pump. The acidosis and hypercapnia resulting would also cause release of catecholamines exacerbating the glycolytic flux and raising blood glucose levels.[11] The membrane changes occurring either due to halothane itself or the consequences of the gross metabolic changes, would further result in the leakage of several cytoplasmic constituents into the plasma.[8]

In order to establish whether the in vitro effects of halothane reported by Eikelenboom and van den Bergh[10] can be produced in vivo, we have taken muscle from pigs before exposure to halothane (under barbiturate anesthesia) and after exposure to halothane and analyzed each biopsy for adenosine triphosphate (ATP), glucose-6-phosphate (G-6-P) and phosphocreatine (PC) concentrations and pH.

## Methods

Twenty-three German Landrace pigs were obtained from a commercial herd with a high incidence of the MH syndrome. The pigs were raised under identical conditions and fed a standard ration.

### Anesthesia

At age 10 to 12 weeks the pigs were anesthetized using pentobarbital sodium. The total anesthetic time was 30 to 35 minutes and approximately 40 mg/kg of body weight of barbiturate was used to maintain anesthesia during this period. After 20 minutes of anesthesia muscle biopsies were taken aseptically and the pigs allowed to recover.

One week after the barbiturate anesthesia, the pigs were exposed to halothane. The halothane was delivered using a semiclosed circuit system, A Fluotec MK III vaporizer (Cyprane Ltd) and a close fitting face mask. Anesthesia was induced using 10% halothane in oxygen at a flow rate of 1.5 to 2 L/min. Within 1 to 2 minutes all animals were comatose and halothane concentrations were reduced to 5%. After a further 1 to 2 minutes the halothane concentration was reduced to 3% for the duration of anesthesia. These concentrations of halothane appear high. However no premedication was used and a high initial concentration was used to produce rapid induction. Further, the semiclosed system used required a slightly raised concentration of halothane for maintenance of anesthesia.

During exposure to halothane rectal temperature was measured using a calibrated laboratory thermometer. In sensitive pigs, halothane anesthesia was discontinued and 100% oxygen administered as soon as rigidity and hyperthermia were observed; the presence of these signs was considered to be pathognomonic. No other tests were done to confirm the presence of the syndrome.

At the onset of rigidity and hyperthermia muscle biopsies were taken. In five of the nine pigs showing typical symptoms further biopsies were taken at intervals until death. All nine pigs that showed typical MH symptoms died after exposure to halothane. The 14 pigs that survived exposure to halothane were classified as MH-resistant. None of the 23 pigs died as a result of barbiturate anesthesia.

### Muscle Biopsies

Muscle obtained during barbiturate anesthesia was taken from the semitendinosus in one limb; the contralateral muscle was used for biopsies obtained during halothane anesthesia. In both cases the muscle was immersed in 10 volumes (per gram of wet weight of muscle) of isopentane in liquid nitrogen at −196 C. This allowed complete freezing of the muscle sample within 5 seconds of excision. The muscle sample was then used for estimation of ATP, G-6-P, and PC using the coupled enzymatic method of Lamprecht and Stein.[12]

Muscle samples used for $pH_0$ (ie, immediate) measurements were homogenized in 10 volumes of 5 mM iodoacetate (pH 7.0) and the pH was measured using a pH meter. Muscle samples used for $pH_1$ (ie, 1 hour after sampling) determinations were incubated for 1 hour in a moist nitrogen atmosphere at 37 C. Thereafter they were treated in the same way as $pH_0$ samples.

### Statistics

Student's *t*-test was used to determine statistical significance. Degrees of freedom were N-2 where N was the number of pigs used in each determination. Not all of the pigs were used for each determination.

## Results

Exposure to halothane identified nine of the 23 pigs as being susceptible to induction of MH by exposure to halothane. The remaining 14 pigs were considered halothane-resistant and were used as the control group.

### Effect of Anesthesia on ATP

Under both barbiturate and halothane anesthesia ATP concentrations are similar (Tables 1 and 2). However, Table 3 shows that in susceptible pigs once MH becomes established ATP concentrations decrease. The difference between ATP levels at the onset of the syndrome ($\bar{x}$ = 5.73 μmol/g) and just before death ($\bar{x}$ = 4.00 μmol/g) is significant ($p < 0.05$).

**TABLE 1**

**Effect of Barbiturate Anesthesia on ATP, G-6-P, PC, and pH***

| Test | Susceptible pigs | Resistant pigs | N | p |
|---|---|---|---|---|
| ATP (μmol/g) | $\bar{x}$ = 5.62 | $\bar{x}$ = 5.66 | | |
| | SD = 1.10 | SD = 1.38 | 20 | NS |
| | SE = 0.36 | SE = 0.37 | | |
| Phosphocreatine (μmol/g) | $\bar{x}$ = 15.80 | $\bar{x}$ = 22.93 | | |
| | SD = 4.79 | SD = 5.71 | 20 | <0.01 |
| | SE = 1.60 | SE = 1.53 | | |
| Glucose-6-phosphate (μmol/g) | $\bar{x}$ = 1.47 | $\bar{x}$ = 0.76 | | |
| | SD = 0.85 | SD = 0.66 | 20 | <0.025 |
| | SE = 0.28 | SE = 0.18 | | |
| $pH_0$ | $\bar{x}$ = 7.08 | $\bar{x}$ = 7.23 | | |
| | SD = 0.10 | SD = 0.11 | 20 | <0.01 |
| | SE = 0.03 | SE = 0.03 | | |
| $pH_1$ | $\bar{x}$ = 6.07 | $\bar{x}$ = 6.48 | | |
| | SD = 0.27 | SD = 0.12 | 20 | <0.001 |
| | SE = 0.09 | SE = 0.03 | | |

* Results were analyzed using Student's *t*-test. $pH_0$ refers to pH measured immediately and $pH_1$ refers to pH measured 1 hour after the muscle sample was taken (see text).

**TABLE 2**

**Effect of Halothane Anesthesia on ATP, G-6-P, PC, and pH**

| Test | Susceptible pigs | Resistant pigs | N | p |
|---|---|---|---|---|
| ATP (μmol/g) | $\bar{x}$ = 5.09 | $\bar{x}$ = 6.10 | | |
| | SD = 1.44 | SD = 2.14 | 20 | NS |
| | SE = 0.48 | SE = 0.59 | | |
| Phosphocreatine (μmol/g) | $\bar{x}$ = 6.30 | $\bar{x}$ = 16.74 | | |
| | SD = 3.16 | SD = 5.88 | 20 | <0.001 |
| | SE = 1.05 | SE = 1.63 | | |
| Glucose-6-phosphate (μmol/g) | $\bar{x}$ = 6.91 | $\bar{x}$ = 2.75 | | |
| | SD = 1.80 | SD = 1.80 | 20 | <0.001 |
| | SE = 0.60 | SE = 0.50 | | |
| $pH_0$ | $\bar{x}$ = 6.42 | $\bar{x}$ = 6.93 | | |
| | SD = 0.17 | SD = 0.09 | 20 | <0.001 |
| | SE = 0.06 | SE = 0.03 | | |
| $pH_1$ | $\bar{x}$ = 5.95 | $\bar{x}$ = 6.07 | | |
| | SD = 0.36 | SD = 0.28 | 15 | NS |
| | SE = 0.15 | SE = 0.12 | | |

**TABLE 3**

**ATP, G-6-P, and PC Concentrations during Malignant Hyperthermia in Susceptible Pigs**

| Pig no. | Time of sample after induction | ATP | G-6-P | PC | Time of death after induction |
|---|---|---|---|---|---|
| | *min* | | *μmol/g* | | *min* |
| 1 | 6 | 6.76 | 5.35 | 8.17 | 19 |
| | 15 | 3.15 | 2.11 | 2.25 | |
| 2 | 5 | 6.49 | 7.89 | 8.45 | 15 |
| | 11 | 6.30 | 6.49 | 6.57 | |
| 3 | 30 | 5.93 | 6.93 | 6.95 | 39 |
| | 34 | 4.63 | 8.33 | 3.57 | |
| 4 | 6 | 4.36 | 8.51 | 3.38 | 16 |
| | 8 | 4.17 | 6.75 | 2.63 | |
| | 15 | 2.32 | 4.65 | 2.16 | |
| 5 | 22 | 5.10 | 8.95 | 4.32 | 27 |
| | 23 | 4.63 | 8.42 | 3.66 | |
| | 26 | 3.61 | 8.33 | 2.54 | |

### Effect of Anesthesia on PC

Under barbiturate anesthesia pigs susceptible to induction of MH by exposure to halothane have significantly lower PC levels than do resistant pigs (Table 1). Under halothane anesthesia the PC levels in susceptible pigs are also significantly lower than in resistant pigs (Table 2). Table 3 shows that during MH phosphocreatine levels in muscle decrease precipitously.

### Effect of Anesthesia on G-6-P

Tables 1 and 2 also show that irrespective of the anesthetic used G-6-P levels are 2- to 3-fold higher in susceptible pigs than in resistant pigs. Absolute levels of G-6-P are higher during halothane anesthesia than during barbiturate anesthesia (Table 4).

### Effect of Anesthesia on muscle pH

Table 1 shows that under barbiturate anesthesia muscle pH of susceptible pigs is significantly lower than that of resistant pigs. A similar difference is observed in muscle pH under halothane anesthesia.

### Effect of Anesthesia on Muscle Metabolism

Table 4 summarizes the effects of halothane on muscle metabolism. In both resistant and susceptible groups of pigs halothane significantly lowers PC levels and pH, and increases G-6-P levels. ATP levels, however, remain unchanged until the syndrome is well established.

### Effect of Halothane on Rectal Temperature

Table 5 shows the effect of halothane anesthesia on rectal temperature. In both MH-resistant and -susceptible pigs initial rectal temperature is similar. However, in susceptible pigs the temperature increases rapidly and within 2 minutes is significantly higher than initial temperature ( $p < 0.01$) and is significantly different ( $p < 0.005$) from the 2-minute temperature of resistant pigs. In the resistant pigs the temperature rises more slowly but by 5 minutes is significantly higher than the initial temperature ( $p < 0.05$). Thereafter the temperature remains stable. In the susceptible pigs the temperature continues to rise and at death (about 20 minutes postinduction) is 3 C higher than initial temperature. This represents a temperature rise of 9 C per hour.

**TABLE 4**

**Effect of Halothane Anesthesia on ATP, G-6-P, PC, and pH in Pigs Resistant to and Susceptible to Induction of MH by Exposure to Halothane**

| Test | Barbiturate | Halothane | N | $p$ |
|---|---|---|---|---|
| ATP ($\mu$mol/g) | | | | |
| Resistant | 5.66 | 6.10 | 25 | NS |
| Susceptible | 5.62 | 5.27 | 16 | NS |
| Phosphocreatine ($\mu$mol/g) | | | | |
| Resistant | 22.93 | 16.74 | 25 | <0.01 |
| Susceptible | 15.80 | 6.51 | 16 | <0.001 |
| Glucose-6-phosphate ($\mu$mol/g) | | | | |
| Resistant | 0.76 | 2.75 | 25 | <0.001 |
| Susceptible | 1.47 | 7.33 | | |
| $pH_0$ | | | | |
| Resistant | 7.23 | 6.93 | 25 | <0.001 |
| Susceptible | 7.08 | 6.42 | 16 | <0.001 |

**TABLE 5**

**Effect of Halothane Anesthesia on Rectal Temperature (Mean)**

| | 0–1 min | 1–2 min | 2–3 min | 5 min | 15 min or death |
|---|---|---|---|---|---|
| Resistant pigs (C) | 39.6 | 39.8 | 39.8 | 40.1 | 40.1 |
| Susceptible pigs (C) | 39.7 | 40.4 | 40.6 | 41.0 | 42.6 |
| $t$ | .3300 | 3.8217 | 5.883 | 5.4216 | 8.6206 |
| N | 20 | 20 | 20 | 20 | 20 |
| $p$ | NS | <0.005 | <0.001 | <0.001 | <0.001 |

## Discussion

The elusiveness of the underlying lesion in MH lies in part in the biphasic nature of the syndrome. The onset is triggered by a variety of agents, especially halothane, and is characterized by a rapid elevation of temperature, by acidosis, and by muscle rigidity. Once initiated the process becomes independent of the tissue concentration of halothane.[8] Muscle is considered to be the site of the primary lesion as this is the most likely source of heat, lactate, and the increased serum levels of creatine phosphokinase characteristic of the syndrome. However, the lesion in muscle remains obscure. It has not been determined whether the defect lies in an abnormal triggering effect produced by the causative agent or whether the syndrome occurs as a result of a lesion not associated with the triggering mechanism.

The results presented in this paper suggest that the effect of halothane on aerobic glycolysis is similar in both MH-susceptible and -resistant animals. It is clear that muscle obtained from resistant pigs exposed in vivo to halothane differs significantly from similar muscle analyzed after 20 minutes of barbiturate anesthesia. The effect of the halothane in resistant pigs is to produce a mild but significant increase in temperature (Table 5), a significant acidosis (Table 4), a significant increase in glycolysis as shown by the elevated G-6-P concentrations (Table 4), and muscle acidosis. The resistant pigs also show a significant decrease in muscle concentrations of PC when exposed to halothane (Table 4). Although ATP concentrations after halothane are not significantly different from concentrations observed during barbiturate anesthesia, the decrease in PC levels after induction of halothane anesthesia suggests a decreased restitution of this high energy phosphate storage compound. Apart from these quantitative effects of halothane we made the clinical observation that during the initial exposure to halothane resistant pigs showed a mild rigidity and peripheral vasoconstriction. All of these events are likely to be due to rapid elevation of myoplasmic calcium levels,[6] although convincing evidence for such an increase is lacking. However, it is important to note that only MH-susceptible pigs die as a result of exposure to halothane. Consequently we conclude from these findings that as both susceptible and resistant pigs have similar initial responses to halothane exposure, the underlying defect resulting in the malignant phase of the syndrome is not due to an abnormal triggering mechanism, but lies elsewhere in the muscle.

The results obtained from susceptible pigs after 20 minutes of barbiturate anesthesia when compared to data obtained from resistant pigs under similar conditions (Table 1) show that susceptible pigs have significant elevations of G-6-P concentrations while muscle pH and PC levels are significantly lower. This suggests that susceptible pigs are always in a state of anaerobic glycolysis. Although ATP concentrations are not significantly different, the lower PC levels suggest that there is either decreased restitution of PC or that PC is contributing to the maintenance of cellular ATP. The increased G-6-P levels suggest that there is an increased glycotic flux which would contribute to the maintenance of ATP levels but which would also lead to the accumulation of lactate if a mitochondrial defect was present.

When susceptible animals are exposed to halothane and the biochemical changes occurring in the muscle are compared to those in muscle obtained after 20 minutes of barbiturate anesthesia (Tables 2 and 4), it is clear that susceptible pigs show the same changes as resistant pigs. However, the decreases in PC and muscle pH and the increase in G-6-P that occur differ significantly from the changes occurring in resistant animals (Table 1) suggesting that the halothane-induced lesion is far more severe in susceptible animals. The characteristic changes seen in both groups of animals are indicative of a retardation or inhibition of mitochondrial respiration. The lesion cannot be in the glycolytic pathway as this is the only source of lactate. The accumulation of G-6-P also suggests an increase in glycogenolysis.

Electron micrographs have shown that the main abnormalities present in skeletal muscle of MH susceptible patients[13] occur in mitochondria. Mitochondria have been found to be in various stages of degeneration so that cristae lie free in the sarcoplasm. It has also been reported that halothane exerts its pathologic effects mainly on the biologic membrane system and organelles.[14] The anesthetic effect of halothane is related to an expansion of cell membranes.[15] As the whole group of pyruvate dehydrogenase enzymes (pyruvate dehydrogenase, dihydrolipoyl transacetylase, dihydrolipoyl dehydrogenase) are known to occur in the mitochondrial membranes, it seems likely that in animals carrying the genetic defect predisposing to MH, halothane causes gross changes in already defective mitochondrial membranes inhibiting dehydrogenation of pyruvate and thus inhibiting aerobic glycolysis. In resistant animals it seems that a similar effect occurs without gross disfiguration of the membranes.

The consequence of inhibition of mitochondrial respiration is decreased mitochondrial synthesis of ATP. Although no significant decreases in ATP were seen in resistant pigs after exposure to halothane, the susceptible animals showed significant decreases in ATP starting 5 to 10 minutes before death (Table 3). Muscle PC concentrations fell concurrently.

These findings suggest that halothane inhibits mitochondrial respiration in pigs in vivo and provide an explanation for the development of the characteristic rigidity, hyperthermia, and acidosis that occur during MH. The rigidity could be due to inactivation of the sarcoplasmic reticulum (SR) calcium pump. Damage to the SR undoubtedly occurs during the syndrome. Inesi, Millman and Eletr[16] have shown that high temperature alters the lipid and protein constitution of the SR. We have shown that calcium uptake by SR is inhibited by halothane and by temperatures of 40–43 C.§ Further, the loss of potassium ions from the sarcoplasm during MH[8] leads to a decrease in calcium uptake by SR.[18] A deficiency of ATP would further inhibit calcium uptake. In addition, ATP protects actomyosin against heat-induced loss of calcium sensitivity in both susceptible and resistant pigs.[19] Thus, if the temperature increases and ATP levels decrease formation of actomyosin will occur independent of calcium concentrations.[19, 20] We have found that magnesium has an effect that is similar to, though less marked than, the effect of ATP at high temperatures (35–40 C) especially if ATP levels are low.[19] As magnesium ions leak into the plasma during MH,[8] low intracellular magnesium may also contribute to the rigidity.

The acidosis occurring during MH is clearly due to retardation or inhibition of dehydrogenation of pyruvate, and the consequent production of lactate. The acidosis potentiates the release of catecholamines which further accelerates glycogenolysis.

---

§ Heffron JJA, Mitchell G: Calcium uptake by sarcoplasmic reticulum of muscle of pigs susceptible to malignant hyperthermia. Proceedings of the International Pig Veterinary Society, 1976.

Perhaps the most difficult characteristic of MH to explain is hyperthermia. In the data reported here temperature increased at a rate of 9 C per hour. In our pigs (average body mass 30 kg) this represents the generation of 250 J/sec additional heat, or the hydrolysis of 0.1 mol of ATP per second. Production of 0.1 mol of ATP requires the aerobic metabolism of 50 g of glucose. It is unlikely that this is the source of heat energy because total body glucose is less than 500 g (10 seconds' supply), and because aerobic metabolism is inhibited. Further, since aerobic metabolism is inhibited hydrolysis of fats cannot contribute to the generation of heat.

For these reasons nonoxidative mechanisms must be at least partly responsible for excess heat production. One source of anaerobic heat is glycolysis. Our results suggest a 2- to 3-fold increase in glycolysis. The release of catecholamines which occurs during MH[21] and which has been considered to be the cardinal event in MH[7] will accelerate glycolytic flux and inhibit heat loss pathways by causing peripheral vasoconstriction. An additional source of heat may be accelerated substrate cycling of fructose-6-phosphate. Halothane has been shown to accelerate substrate cycling in susceptible pigs.[22] Last, hydrolysis of high energy phosphate compounds will yield heat. Our results show that PC levels fall rapidly after exposure to halothane.

From these results we suggest then, that the key event in MH is the rapid onset of anaerobic glycolysis. The most likely mechanism of onset is rupture of mitochondrial membranes and inhibition of pyruvate dehydrogeneration. This leads to formation of lactate, decreased synthesis of ATP, and decreased restitution of phosphocreatine. The release of catecholamines and an increase in membrane permeability potentiate these effects and produce rigidity, hyperthermia, and acidosis.

These results also suggest that skeletal muscles of MH-susceptible pigs are in a state of anaerobic respiration even before exposure to halothane. It is, therefore, clear that any excessive nervous activity caused by stress or exercise will exacerbate the condition Further, although it seems likely that halothane both initiates and potentiates the syndrome any substance which *etiher* initiates muscle contraction or disturbs the integrity of organelle membranes will precipitate the syndrome in susceptible animals. This observation could help to explain why a very wide range of drugs have been shown to cause MH. Most commonly these agents are anesthetics, and it is now well established that there is a good correlation between lipid solubility and anesthetic activity. Nonanesthetic drugs (e.g. succinylcholine) on the other hand will produce MH by initiating muscle contraction.

Finally muscle represents the largest mass of tissue, and consequently interference with metabolic pathways in muscle can produce metabolic changes affecting the whole body. However, we must conclude that mitochondria in all tissues will be affected by halothane with detrimental effects to the metabolism of these tissues.

## ACKNOWLEDGMENT

We thank Dr. R. T. Naude of the Animal and Dairy Science Research Institute, Irene, South Africa, for help and advice.

## REFERENCES

1. Britt BA, Kalow W, et al: Malignant hyperthermia: an investigation of five patients. Can Anaesth Soc J 20:431–467, 1973
2. Mitchell G, Heffron JJA: Procaine in porcine malignant hyperthermia. Br J Anaesth 6:667–668, 1975
3. Hall GM, Lister D: Procaine and malignant hyperthermia. Lancet 1:208, 1974
4. Hall LW, Trim CM, Woolf N: Further studies of porcine malignant hyperthermia. Br Med J 2:145–148, 1972
5. Maclachlan D, Forrest AL: Procaine and malignant hyperthermia. Lancet 1:355, 1974
6. Britt BA: Etiology and pathophysiology of malignant hyperthermia. Fed Proc 38:44–48, 1979
7. Williams CH, Houchins C, Shanklin MD: Pigs susceptible to energy metabolism in the fulminant hyperthermia stress syndrome. Br Med J 3:411–413, 1975
8. Berman MC, Harrison G, Bull AB, et al: Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. Nature 225:653–655, 1970
9. Relton JES, Britt BA, Steward DJ: Malignant hyperpyrexia. Br J Anaesth 45:269–275, 1973
10. Eikelenboom G, van den Bergh SG: Aberrant mitochondrial energy metabolism in stress-susceptible pigs. Second International Symposium on Condition and Meat Quality in Pigs. Edited by JCM Hessel-de-Heer, et al. Holland, Pudoc Press, 1971, pp 66–72
11. Hall GM, Lucke JN, Lister D: Treatment of porcine malignant hyperthermia. Anaesthesia 30:308–317, 1975
12. Lamprecht W, Stern P: Creatine phosphate, in Methods of Enzymatic Analysis. Edited by H-U Bergmeyer. New York, Academic Press, 1975, p 610–616
13. Isaacs H, Frere G, Mitchell JA: Histological, histochemical and ultramicroscopic findings in muscle biopsies from carriers of the trait for malignant hyperpyrexia. Br J Anaesth 45: 860–868, 1973
14. Chang LW, Dudley AW, Lee YK, et al: Ultrastructural changes in the kidney following chronic exposure to low levels of halothane. Am J Pathol 78:225–242, 1975
15. Glauber HS: Mechanisms of action of inhalational anaesthetics. S Afr Med Sciences 41:305–326, 1976
16. Inesi G, Millman M, Eletr S: Temperature induced transitions of function and structure in sarcoplasmic reticulum membranes. J Mol Biol 81:483–504, 1973
17. Deleted in proof

18. Browne S, Duggan PF: Sarcoplasmic reticulum vesicles: a model system for anaesthesia studies. Biochem Soc Trans 2:1383–1385, 1975
19. Green R, Mitchell G, Heffron JJA: Effects of temperature, adenosine triphosphate and magnesium concentrations on the contraction of actomyosin isolated from halothane sensitive and insensitive German Landrace pigs. Br J Anaesth, in press 1980
20. Fuchs F: Thermal inactivation of the calcium regulatory mechanism of human skeletal muscle actomyosin: a possible contributing factor in the rigidity of malignant hyperthermia. Anesthesiology 42:584–589, 1975
21. Lucke JN, Hall GM, Lister D: Porcine malignant hyperthermia. I. Metabolic and physiological changes. Br J Anaesth 48: 297–304, 1976
22. Clark MG, Williams CH, Pfeifer WF, et al: Accelerated substrate cycling of G-6-P in the muscle of MH pigs. Nature 245: 99–101, 1973

---

## Use of PEEP After Open Heart Surgery

The efficacy of routine therapy with positive end-expiratory pressure (PEEP) following open heart surgery was evaluated in 24 patients during mechanical ventilation. The goal of therapy was prevention of left lower lobe atelectasis. Patients were randomly assigned to either a group receiving therapy with PEEP (10 patients) or to a group without PEEP (14 patients). The two groups could not be distinguished by age, weight, the forced expiratory volume in 1 second ($FEV_1$), the ratio of $FEV_1$ to the forced vital capacity, the time on bypass, the units of blood transfused, the tidal volume, or the duration of mechanical ventilation. There was no significant roentgenographic difference between the two groups in either the degree or frequency of left lower lobe atelectasis. While the arterial-alveolar oxygen ratios tended to improve over time in those patients receiving PEEP, this improvement was not clinically significant. No complications were encountered with the use of PEEP. The authors conclude that the routine use of PEEP following open heart surgery is safe but offers no advantage over standard ventilatory techniques. *(Good JR, Wolz JF, Anderson JT, et al: The routine use of positive end-expiratory pressure after open heart surgery. Chest 76:397–400, 1979)*
*See also—Editorial. O'Donohue WJ: Positive end-expiratory pressure is no panacea. Chest 76:373–374, 1979*

ANESTH ANALG
59:257-262, 1980

# Myocardial Reinfarction following Local Anesthesia for Ophthalmic Surgery

**Carl L. Backer, BA,* John H. Tinker, MD,† Dennis M. Robertson, MD,‡ and Ronald E. Vlietstra, MB, ChB§**

---

BACKER, C. L., TINKER, J. H., ROBERTSON, D. M., AND VLIETSTRA, R. E. Myocardial reinfarction following local anesthesia for ophthalmic surgery. Anesth Analg 59:257-262, 1980.

During the years 1962 through 1977, more than 10,000 ophthalmic operations at our institution were managed with local anesthesia and/or retrobulbar block. Of these, 195 patients who underwent 288 separate operations had previously suffered a documented myocardial infarction (MI). Not a single postoperative reinfarction or death occurred in this group. During the same period, only 26 such operations were performed on 21 patients with prior MI under general anesthesia. This much smaller group also suffered no perioperative reinfarctions. This zero percent reinfarction rate is significantly less than the 6.1% reinfarction rate previously reported from this institution for 587 operations on patients with documented preoperative MI who had general or major regional anesthesia for nonophthalmic surgery. In the prior study, intrathoracic, upper abdominal, and great vessel operations, lasting 3 hours or more, were associated with significantly greater reinfarction rates than the total population. Eliminating these from the prior series yields a 3.6% reinfarction rate for all other operations, which is still significantly greater than the zero reinfarction in the present series of ophthalmic procedures. The group that had general anesthesia for ophthalmic surgery is too small for meaningful comparisons, and we cannot conclude that local is safer than general anesthesia. We do conclude that local anesthesia and/or retrobulbar block for ophthalmic surgery does not pose special risks for reinfarction in the patient with a preoperative MI.

**Key Words:** HEART: infarction; ANESTHESIA: ophthalmologic; SURGERY: ophthalmologic.

---

MYOCARDIAL infarction (MI) during and following general and major regional anesthesia has been reported to occur at a rate of approximately 6% in patients who have either a documented prior MI[1,2] or angiographically documented coronary artery disease (CAD).[3] If the previous infarct occurred less than 3 months before anesthesia and surgery, reinfarction rates as high as 27% and 37%[1,4] have been reported The reinfarction rate decreased to between 11% and 16% if the prior MI was 3 to 6 months old, and stabilized at about 6% in patients with infarcts older than 6 months.[1,4] Patients without preoperative MI or CAD have considerably less risk of intra- or postoperative MI (approximately 0.13%).[4,5]

The present study was undertaken to determine whether local anesthesia was associated with similar reinfarction rates during and following surgery in these apparently high risk patients. We chose to study patients undergoing major ophthalmic operations because these surgical procedures are generally performed at our institution using local anesthesia (local infiltration, retrobulbar block, and/or facial nerve block).[6] These patients, often elderly, conceivably

---

* Medical Student.

† Associate Professor of Anesthesiology.

‡ Associate Professor of Ophthalmology

§ Assistant Professor of Medicine

Supported in part by Grant NIGMS 24531 from the National Institutes of Health.

Received from the Departments of Anesthesiology, Ophthalmology, and Internal Medicine (Cardiovascular Disease Division), Mayo Clinic and Mayo Medical School, Rochester, Minnesota 55901. Accepted for publication December 27, 1979.

anxious about undergoing major eye surgery while awake, represent a group that might be expected to undergo relatively great stress during surgery.[7] Not surprisingly, peri- and postoperative MIs have been reported to comprise a significant source of postoperative mortality in this group.[8]

## Methods

Utilizing the computerized listing of operations performed at the Mayo Clinic, we identified 10,278 ophthalmic operations of types likely to have been performed under local/or retrobulbar block anesthesia during the 15 years from 1962 to 1977 inclusive. These records were then computer-scanned for a pre- or postoperative diagnosis of coronary artery disease. The 970 records so identified were individually reviewed in detail. A preoperative MI had been diagnosed in 195 patients by either: (1) unequivocal findings of MI in the 12-lead preoperative electrocardiogram (67%); or (2) appropriate history accompanied by unequivocal earlier ECG (27%) or changes in levels of blood enzymes typical of MI (6%). ECGs from other institutions were evaluated only when the actual tracing could be obtained. This definition of a prior MI is consistent with that of the World Health Organization.[9]

Patient data recorded for those with a prior MI included age, sex, time interval from prior MI, site of prior MI, and relevant preoperative medical problems such as diabetes and/or angina. Also noted were type of surgery, preoperative medication, American Society of Anesthesiologists (A.S.A.) physical status, anesthetic technique including intravenous sedatives and/or narcotics, duration of the surgery and the procedure, and duration of postoperative follow-up. Evidence for postoperative reinfarction on postoperative days 0 to 7 was sought by chart review for historical, electrocardiographic, and/or enzymatic changes indicative of infarction.

We were concerned with documenting each patient's intraoperative course for the development of tachycardia, bradycardia, hypotension, or hypertension. These four conditions were arbitrarily defined as a 30% change in the pulse rate or systolic blood pressure from the value obtained immediately preoperatively persisting for 10 minutes or longer during anesthesia and surgery.

The results of this review were then compared with a previous study from this institution for the years 1974 and 1975 on patients with identically documented prior MI who underwent noncardiac, nonopthalmic surgery under general or major regional anesthesia.[1] Analysis was by either chi-square test or Student's *t*-test, where appropriate, with $p < 0.05$ considered significant.

## Results

From 1962 through 1977, 195 patients undergoing 288 ophthalmologic operations under local anesthesia had suffered a documented MI preoperatively (Table 1). Not a single postoperative reinfarction or death occurred in this group. Two hundred fifty-five other patients undergoing 373 operations under local anesthesia had preoperative CAD manifested by angina pectoris but without definite evidence of MI. Two of these patients (0.54%) had a postoperative MI; neither died. Two other patients from this latter subgroup died suddenly postoperatively between postoperative days 4 and 7, but an autopsy was not performed. Of the 9,617 ophthalmic procedures performed with local anesthesia in patients without documented evidence of preoperative CAD or MI, only one patient (0.01%) suffered a postoperative MI. During this same time period only 26 similar ophthalmic operations were performed on 21 patients with a preoperative MI under general anesthesia. No postoperative MI occurred in this small group, either.

Men (n = 200) constituted 69% of the population of operations on patients with documented prior MI. Ninety percent of the population (male and female) was 60 years of of age or older; the average age was 72 (Table 2). Of the population with prior MI 18% also had preoperative diabetes; 40% had angina by history in addition to prior MI. We made no attempt to assess adequacy of preoperative control of any of these co-existing conditions.

Prior infarcts were categorized as anterior (130 operations or 45%), inferior (90 or 31%), posterior (19 or 8%), anterior plus inferior (6 or 2%) and subendocar-

**TABLE 1**

**Relation of Preoperative Physical Condition to Postoperative Myocardial Infarction (MI) and Death Among Patients Having Ophthalmic Surgery with Local Anesthesia**

| Preoperative condition | No. of operations | Postoperative MI | Postoperative death |
|---|---|---|---|
| Prior MI | 288 | 0 | 0 |
| Suspected CAD,* no evidence MI | 373 | 2 (0.54%)† | 2 (0.54%)† |
| No evidence prior CAD or MI | 9,617 | 1 (0.01%) | Not examined |

* CAD, Coronary artery disease.
† Four different patients.

**TABLE 2**

**Age Distribution of Population**

| Age | No. of operations |
|---|---|
| 0–49 | 1 (0.3%) |
| 50–59 | 33 (11%) |
| 60–69 | 78 (27%) |
| 70–79 | 124 (43%) |
| 80–89 | 49 (17%) |
| 90–99 | 3 (1%) |

**TABLE 3**

**Types of Procedures**

| Procedure | No. of operations |
|---|---|
| Cataract extraction | 207 (72%) |
| Retinal detachment | 11 (4%) |
| Other intraocular | 11 (4%) |
| Plastic lid procedure | 53 (18%) |
| Miscellaneous | 6 (2%) |

**TABLE 4**

**Preoperative Physical Status**

| A.S.A. physical status | No. of operations (%) |
|---|---|
| 1 | 19 (6%) |
| 2 | 97 (34%) |
| 3 | 145 (50%) |
| 4 | 8 (2%) |
| 5 | 0 |
| Unrecorded | 19 (7%) |

dial (13 or 5%). The location was uncertain in 30 patients (9%).

Because of the elective nature of most of these procedures, only nine operations were performed within 3 months of a verified MI, and only nine others within 3 to 6 months of an MI. None of these 18 procedures was associated with reinfarction.

There were numerous minor operations performed in the ophthalmologists' offices (including "one snip") procedures, chalazion removal, photocoagulation, etc). Twenty-one such operations were performed on patients with verified prior MI, without any recorded reinfarctions. These operations are not included in the tabulated results because there were no anesthesia personnel involved, and no vital sign records were available.

All operations included in this review were performed in an operating room. "Local standby" at our institution means an anesthesiologist, resident, or nurse anesthetist physically present in the operating room at all times, with vital signs recorded every 5 minutes, and a standard anesthesia record completed. ECG monitoring was standard in later years. Supplemental oxygen was often administered. Eighty percent of these operations were for cataracts, retinal detachment, or other major intraocular problems (Table 3).

Preoperative medication varied greatly, but usually included both a sedative/hypnotic and narcotic. Prior to 1974 ethchlorvynol (200 to 600 mg IM 2 to 3 hours prior to surgery) was the most commonly used sedative; it was generally replaced in later years by diazepam (5 to 10 mg IM 2 to 3 hours prior to surgery). Levorphanol 1 to 2.5 mg IM 1 to 3 hours prior to surgery) and meperidine (25 to 75 mg IM 1 to 3 hours prior to surgery) were the most commonly used narcotics. Although 84% of the patients with verified prior MI were categorized preoperatively by the staff anesthesiologist or resident as A.S.A. class 2 or 3, patients were placed in A.S.A. Class 1, despite prior MI, before 19 operations (see Table 4). Eight patients were A.S.A. class 4.

The details of the anesthetic depended on the type and extent of the procedure. Intraocular procedures were performed with facial nerve blocks and retrobulbar injection, usually with 2% lidocaine with epinephrine (1:100,000). Total volumes injected varied from 5 to 10 ml. Lid procedures were performed with field blocks, again with 2% lidocaine plus epinephrine (1:100,000). Volumes of anesthetic solution for lid procedures (n = 53) ranged from 2 to 10 ml.

Of the procedures 106 (37%) required less than 1 hour to complete; 149 (52%) required 1 to 2 hours. Thus, 89% of the procedures lasted less than 2 hours. Average duration of anesthesia and surgery was 68 ± 2 minutes (SEM). Time from incision to completion of closure averaged 44 minutes (Table 5).

Intraoperatively, hypertension (defined above) occurred during 28 procedures (9.7%) and hypotension during 12 (3.9%). Tachycardia occurred during 2.3% of the procedures and bradycardia during 2.9%.

No evidence regarding ventilation other than repiratory rate could be obtained from the records. There were no recorded instances of acute respiratory distress, respiratory arrest, or the need for assisted or controlled ventilation. There were no intraoperative cardiac arrests. Narcotic antagonists were only occasionally employed.

## Discussion

We considered the 288 operations rather than the 195 patients as separate entities for statistical analysis because the procedures were performed at different times and each constituted a separate risk. Comparison of the zero reinfarction rate in these 288 ophthal-

**TABLE 5**
**Duration of Procedures**

| Procedure duration | No. of operations (%) |
|---|---|
| 0–1 hr | 106 (37%) |
| 1–2 hr | 149 (52%) |
| >2 hr | 15 (5%) |
| No record | 18 (6%) |

**TABLE 6**
**Relation of Myocardial Reinfarction (MI) to Preoperative Condition, Type of Anesthesia, and Length and Type of Procedure**

| Preoperative condition | Population | Anesthesia | Reinfarction (%) |
|---|---|---|---|
| Documented prior MI | 288 | Local | 0 |
| | 587 | General | 36 (6.1%) |
| Documented prior MI; procedure 1–2 hr | 149 | Local | 0 |
| | 182 | General | 6 (3.3%) |
| Documented prior MI; procedure 1–3 hr; not thoracic, upper abdominal or great vessel | 164 | Local | 0 |
| | 329 | General | 12 (3.6%) |

mic operations performed on 195 patients under local anesthesia with the 6.1% reinfarction rate previously reported[1] for 587 operations on patients with prior MI who underwent noncardiac procedures under general or major regional anesthesia indicates the difference to be highly significant ( $p < 0.001$ by chi-square test). Two postoperative myocardial infarctions did occur in 255 other patients (373 operations) in whom CAD was suspected or suggested, but who did not have a verifiable prior MI. This 0.54% incidence is not large enough to permit the speculation that perhaps CAD without MI is a greater risk than a "completed" MI.

Obviously there are many complex differences between operations performed under general and local anesthesia. We examined several important risk factors found to correlate positively with the reinfarction rate in the previous study and attempted to correct for these factors by dividing both the local anesthesia-ophthalmic surgery group and the general anesthesia group into more appropriate subgroups.

The previous study[1] reported a positive correlation between reinfarction risk and duration of anesthesia and surgery (almost a linear function), especially if the procedure was thoracic, upper abdominal, upon the great vessels, and longer than 3 hours. Because most of the ophthalmic procedures lasted less than 2 hours, we corrected for duration of anesthesia by comparing only procedures in the two separate groups lasting between 1 and 2 hours. The reinfarction rate for ophthalmic procedures under local anesthesia is still significantly lower than that for procedures of similar duration under general or major regional anesthesia (0% vs 3.3%,[1] $p < 0.05$). Breakdown of the "general anesthesia" group in a different way by eliminating all higher risk intrathoracic, upper abdominal, great vessel, and lengthy (greater than 3 hours) operations again indicates the reinfarction rate associated with local anesthesia for ophthalmic surgery to be significantly lower (0% vs 3.6%,[1] $p < 0.01$) (Table 6).

Other variables associated with significantly increased reinfarction rates under general anesthesia included preoperative hypertension, intraoperative hypotensive episodes, and recent prior MI.[1] Preoperative hypertension was not examined in the present study. No reinfarctions occurred following the 12 procedures (3.9%) with intraoperative hypotension or in the groups with MIs either 3 months or less preoperatively (nine procedures) or 3 to 6 months preoperatively (nine procedures). This contrasts with the previously reported group of patients undergoing noncardiac surgery under general or major regional anesthesia in which reinfarction rates of 27% and 11% were noted for the above two time periods, respectively.[1] The difference between the zero reinfarctions in 18 operations in patients having local anesthesia with infarcts less than 6 months old and the six reinfarctions reported in 33 operations in patients with infarcts of similar age having general anesthesia is of borderline statistical significance (0% vs 18%, $p = 0.054$, chi-square test).

The ophthalmic surgical patients had about the same incidence of diabetes (18% vs 21%) and angina (40% vs 34%) as the previous study population, as well as similar sex ratios (69% vs 79% males) and infarct location patterns. Ophthalmic patients were significantly older (mean of 72 vs 67, $p < 0.001$).

The above findings are subject to a number of potential errors. The study was retrospective and therefore some patients with prior MI who underwent ophthalmic surgery might have been missed. However, all patients more than 40 years of age undergoing surgery were required to have a preoperative ECG which was read by a cardiologist. Obviously various types of MIs, especially subendocardial infarctions, could have been missed, but we see no reason why this error should be different in the groups having general or local anesthesia.

Another possible error relates to the early discharge of ophthalmic patients from the hospital before 7 postoperative days have passed. The average hospital stay after the 288 ophthalmic operations on patients with verified prior MIs was 3 days. Nonetheless, these patients were followed regularly as outpatients for an average of 10 days by their ophthalmologists for evaluation of a number of possible complications that could lead to loss of vision. We feel this was an adequate avenue for the reporting of significant chest pain or other symptoms. The possibility of a "silent" postoperative MI is not considered common and was just as likely in the previous study. Positively, the retrospective nature of such a study, while failing to allow controlled design, nonetheless does not suffer from the possibility that clinical practices may be altered merely by the knowledge that such a study is underway.[10]

The present series was obtained during the years 1962 through 1977. The "general" anesthesia series[1] was obtained from 1974 through 1975. Although the data bases thus differ, the incidence of reinfarction in the 1974 to 1975 patients did not differ significantly from that reported by Tarhan et al[4] from our institution in patients anesthetized during 1967 and 1968. Also, the near zero overall incidence of postoperative reinfarction, reported herein over a 15-year period negates the likelihood of significant changes in incidence occurring with time.

Another potential criticism of the comparison is the possibility that the relatively high (6%) incidence of reinfarction associated with general anesthesia was higher than would be expected nationally. Against this is the rather general agreement represented by the 6% reinfarction incidence reported in other retrospective studies.[2, 11] Prospective studies have reported a similar increased incidence of reinfarction in patients with prior MI.[12]

With respect to ophthalmic surgery, several studies have recommended that general anesthesia be used for all but the most trivial ophthalmic procedures.[7, 13, 14] Two studies[15, 16] that have compiled overall mortality rates for general vs local anesthesia in ophthalmic surgery have concluded that there is little difference in terms of morbidity and mortality following ophthalmic surgery performed with general or local anesthesia. In these two studies, however, the potentially high risk groups of patients with prior MI were not evaluated separately. Wolf et al[17] reported on 2,217 patients who had surgery under general anesthesia with excellent results. Sixty-four of these patients had suffered a prior MI, and there was one possible postoperative infarction reported. With this small number of patients a statistically significant difference cannot be demonstrated since the expected incidence of reinfarction is only 6%.

Because so few patients with a prior MI in our study had general anesthesia (21 patients, 26 operations), we cannot categorically conclude that local anesthesia in these patients is safer than general or major regional anesthesia. Nonetheless, the reinfarction incidence in patients with prior MI undergoing general anesthesia for less than 3 hours who did not have intrathoracic, great vessel, or upper abdominal procedures was still significantly higher than the zero incidence in our significantly older ophthalmic patients with prior MIs who had local anesthesia. Clearly, a direct comparison of local vs general anesthesia, among similar patients having similar procedures by the same surgeons at the same institution, would be required to prove whether the type of anesthesia or the type of procedure is the most important factor accounting for differences in reinfarction rate. Based on our findings that potentially high risk ophthalmic patients with a preoperative MI do well with local anesthesia we would tend to continue that practice. We conclude that ophthalmic procedures can be performed under local anesthesia and/or retrobulbar block with trivial risk of perioperative reinfarction in patients who have suffered a prior MI.

## ACKNOWLEDGMENT

The authors thank William F. Taylor, PhD, Department of Statistics, for performing the statistical analyses.

## REFERENCES

1. Steen PA, Tinker JH, Tarhan S: Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566–2570, 1978
2. Topkins MJ, Artusio JF: Myocardial infarction and surgery. Anesth Analg 43:716–720, 1964
3. Mahar LJ, Steen PA, Tinker JH, et al: Perioperative myocardial infarction in patients with coronary artery disease with and without aorto-coronary bypass grafts. J Thorac Cardiovasc Surg 76:533–537, 1978
4. Tarhan S, Moffitt EA, Taylor WF, et al: Myocardial infarction after general anesthesia. JAMA 220:1451–1454, 1972
5. Plumlee JE, Boettner RB: Myocardial infarction during and following anesthesia and operation. South Med J 65:886–889, 1972
6. Atkinson WS: Anesthesia in Ophthalmology. Springfield, IL, Charles C Thomas, 1955
7. Goldsmith E: General anesthesia in 350 cataract extractions. Anaesthesia 16:241–246, 1961
8. Quigley HA: Mortality associated with ophthalmic surgery. Am J Ophthalmol 77:517–524, 1974
9. WHO Task Force: Nomenclature and criteria for diagnoses of ischemic heart disease. Circulation 59:607–608, 1979
10. Little JB, Radford EP: Effects of ionizing radiation and their

importance in anesthesiology. Anesthesiology 25:479–489, 1964

11. Mauney FM, Ebert PA, Sabiston DC: Postoperative myocardial infarction. Ann Surg 172:497–503, 1970
12. Goldman L, Caldera DL, Nussbaum SR, et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845–850, 1977
13. Mehta M: General anesthesia in intra-ocular surgery. Br J Clin Pract 16:339–342, 1962
14. Rosen DA: Anesthesia in ophthalmology. Can Anaesth Soc J 9:545–547, 1962
15. Petruścak J, Smith RB, Breslin P: Mortality related to ophthalmological surgery. Arch Ophthalmol 89:106–109, 1973
16. Duncalf D, Gartner S, Carol B: Mortality in association with ophthalmic surgery. Am J Ophthalmol 69:610–615, 1970
17. Wolf GL, Lynch S, Berlin I: Intra-ocular surgery with general anesthesia. Arch Ophthalmol 93:323–326, 1975

---

## Pneumopericardium following Laparoscopy

Pneumopericardium and subcutaneous emphysema developed several hours following an otherwise uncomplicated laparoscopic tubal ligation. Under general anesthesia, with endotracheal intubation and mechanical ventilation, laparoscopy was performed using a Veress needle and insufflation with 5 L of carbon dioxide. Following coagulation of the Fallopian tubes, the abdomen was desufflated and the incisions were closed. Awakening from anesthesia was without incident. About 6 hours after the procedure the patient complained of chest pain. Subcutaneous emphysema was present in the neck and anterior chest, but not in the abdominal wall. There was clinical and x-ray evidence of pneumopericardium, without a pneumothorax. No specific therapy was required. By the fourth postoperative day physical examination was normal except for localized subcutaneous emphysema above the clavicles. Pneumopericardium appears to be an alarming but benign rare complication of laparoscopy. *(Nicholson RD, Berman ND: Pneumopericardium following laparoscopy. Chest 76:605–607, 1979)*

ANESTH ANALG
59:263-269, 1980

# Noninvasive Measurement of Pulmonary Gas Exchange during General Anesthesia

**Frances E. Noe, MD,[*] Albert J. Whitty, PhD,[†] Kenneth R. Davies, BA,[‡] and Barbara L. Wickham, BS[§]**

---

NOE, F. E., WHITTY, A. J., DAVIES, K. R., AND WICKHAM, B. L.: Noninvasive measurement of pulmonary gas exchange during general anesthesia. Anesth Analg 59:263–269, 1980.

Expired gas flow volume ($\dot{V}_E$), carbon dioxide excretion ($\dot{V}_{CO_2}$) and oxygen consumption ($\dot{V}_{O_2}$) were measured continuously for 2-minute periods at 15-minute intervals during at least 75 minutes of general anesthesia and surgery in clinical patients. Analog tape-recorded outputs from an infrared $CO_2$ analyzer, from a rapid polarographic $O_2$ analyzer, and from a pneumotachograph were subsequently processed by a general purpose digital computer. Values for $\dot{V}_E$, $\dot{V}_{CO_2}$, and $\dot{V}_{O_2}$ in a group of 50 normal paralyzed endotracheally intubated women with balanced $N_2O$-$O_2$-fentanyl anesthesia for lower abdominal surgery compare favorably with the few published reports of similar measurements. The measured response to anesthesia and surgery in most patients included a progressive increase in $O_2$ uptake and a concurrent but not necessarily simultaneous decrease in $CO_2$ output with a consequent decreased respiratory gas exchange ratio ($R_E$).

**Key Words:** MEASUREMENT TECHNIQUES: pulmonary gas exchange; CARBON DIOXIDE: output; OXYGEN: uptake.

---

COMPUTER-ASSISTED measurement of the volume of expired gases provides a rapid and reproducible method for monitoring patients during critical care and anesthesia. Adequate gas exchange at the pulmonary level indicates that during anesthesia basal metabolism is not overly depressed, tissue perfusion and cardiac function are not compromised, and pulmonary perfusion and ventilation meet physiologic demands. Acute changes in the volumes of expired gases will give rapid warning of drastic circulatory or pulmonary incidents such as air embolus or pulmonary infarct. Less rapid changes may indicate the development of hypoxemia, malignant hyperthermia, or hypovolemia.

Noninvasive monitoring of cardiopulmonary function and metabolism is widely applicable in both anesthesia practice and critical care medicine. Where arterial and mixed venous blood samples are available, the measurement of pulmonary gas exchange can be used to calculate cardiac output with either or both $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ using the Fick equation.

The clinical studies included in this report were chosen from data from more than 200 patients obtained during anesthesia and surgery of at least 75 minutes duration. With the exception of the total hip case included with the case reports, all of the present data were obtained from endotracheally intubated subjects who were mechanically ventilated during drug-induced muscular relaxation and balanced anesthesia. Data from a group of 50 normal women during lower abdominal surgery show the change in measured values with the duration of anesthesia and

---

[*] Attending Staff, Sinai Hospital; Assistant Professor, Department of Anesthesiology, Wayne State University.

[†] Acting Chairman, Department of Research, Sinai Hospital; Associate Professor, Department of Physiology, Wayne State University.

[‡] Research Fellow, Sinai Hospital.

[§] Staff Research Associate, Sinai Hospital.

Received from the Departments of Anesthesiology and Research, Sinai Hospital of Detroit, Detroit, Michigan 48235. Accepted for publication December 6, 1979.

Reprint requests to Dr. Noe.

propose a normal range of values for monitoring pulmonary gas exchange.

## Methods

The basic measuring system consists of three simultaneous continuous measurements from the expiratory flow of each breath: the $CO_2$ concentration measured with an infrared $CO_2$ analyzer (Godart KK), the $O_2$ concentration measured with a rapid polarographic analyzer (Beckman OM-11), and the gas flow rate measured by a pneumotachograph (Fleisch 100-liter with Statham PM-97 differential pressure manometer). The signals from these instruments were recorded simultaneously on tape using an FM analog tape recorder (Honeywell C-5600) or, currently, are introduced directly into a portable digital microcomputer.

The computer conversion of taped analog data to physiologic values requires three individual computer programs. The first stage or phase is the necessary conversion of the analog recording to digital data. Conversion consists of taking sample voltages of the analog tape at a rate of 40 Hz and converting them into an eight-character binary bit which is recorded in the computer memory. At each sampling of the analog tape the three channels of data are read simultaneously and an identifying line number is recorded in a fourth channel by the computer. This process takes no more time than did the original recording and the subsequent digital recording may be stored indefinitely.

The program for the second stage of computation transfers the calibration data into the computer memory. The tape is read and recorded; plateaus are recorded as numbers for three or more gas flow rates for the flow meter and standard gas concentrations for the gas analyzers. These digital numbers from the calibration plateaus are simultaneously entered into a polynomial fit program with the original calibration gas and flow data. From this program are derived the necessary coefficients for a polynomial equation to reconvert the digitalized data that has been stored in the computer memory to the original gas percents and flow rates.

The third computer program runs the digitized tape data through the computer, monitoring the air flow channel for numbers of a significant level. This eliminates most errors due to signal noise or other artifacts on the tape and signals the beginning of a breath. When the numbers decrease in value below the significant level, the computer notes this as the termination of the breath. This simple system of identification and position cannot be used for the gas concentration channels. The instruments' response time lags are minimal, fractions of a second, but the transition time from introduction of the breath sample to arrival at the detection cells is considerable, especially in surgery where space is restricted and longer transit tubes are required. Our laboratory studies indicate that these longer transit tubes do not modify significantly the volumes of gases measured with the system. These lags are determined in each clinical case and are entered manually into the computer, which is programmed to shift the data in each gas channel to the appropriate real time of the breath. The significant increase in numbers in the gas concentration channels begins after the initial dead space of the breath has been computed in the air flow or gas flow channel.

The ultimate computer calculation is the multiplication of the gas flow rate at each 1/40th second by the corresponding $CO_2$ concentration and the $O_2$ concentration obtained by subtracting the recorded concentration from the inspired $O_2$ concentration. The gas flow rate is simultaneously integrated using Euler's method to obtain the gas flow volume which is summated to indicate the total volume of gas expired up to any instant in the expiration cycle. These data and the corresponding $CO_2$ and $O_2$ volumes for each 1/40th of a second can be plotted to give a profile of gas consumption or excretion for each breath. Details of these procedures have been published elsewhere.[1]

Appropriate calibrations with assayed gas mixtures for the gas analyzers and constant gas flows, including anesthetic gases from the anesthesia machine measured with a National Instruments Laboratories Vol-o-flo ball-type flow meter for the pneumotachograph calibration, were entered into the computer in each case. The volume of ventilation for each patient was determined by the clinical ventilator volume set for each case, usually approximately 10 ml/kg. This resulted in considerable variation for individual cases which was not immediately apparent due to the necessary delay in processing taped data.

Taped data were collected continuously for 2-minute periods at 15-minute intervals during clinical anesthesia from the time of endotracheal intubation to the end of the surgical procedure. The time intervals were varied slightly to obtain as steady a state as possible during anesthesia and surgery. The patients received narcotic-hydroxyzine-glycopyrrolate premedication and sodium thiopental-$O_2$ induction with succinylcholine preceded by curare for muscle relaxation and intubation. Anesthesia was maintained with $N_2O$-fentanyl and tubocurarine or pancuronium bromide for muscle relaxation throughout the case. Institutional approval for this investigation and informed consent were obtained.

In order to obtain a range of values for pulmonary gas exchange during anesthesia in normal women, a control group of 50 cases were anesthetized by the same anesthesiologist using comparable anesthetic procedure insofar as possible. Drug dosage was governed by the conduction of the case, not by calculated amounts by weight. Cases with undue blood loss, hypotension, or resistance to drugs, requiring larger than usual dosages, were eliminated from the study. Due to the lack of a suitable $O_2$ analyzer, only $\dot{V}_E$ and $\dot{V}_{CO_2}$ were measured for the initial cases. The measurement of both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ was obtained in 27 cases, which included 12 patients in the control group.

## Results

The mean pulmonary $CO_2$ excretion per minute during general anesthesia with mechanical ventilation for lower abdominal surgery in 50 normal women measured after each of five 15-minute periods of anesthesia is given in Table 1. This table also shows these values corrected for the body surface area (BSA) in square meters ($m^2$).

Table 2 gives the measured pulmonary gas exchange for each of 12 patients of the study group where both $CO_2$ and $O_2$ uptake were computed simultaneously. The Figure shows the means and standard deviation for these values corrected for BSA in square meters of each patient and plotted for each time interval.

It is evident from these data that measured values for $CO_2$ output decreased during the 1st hour of general anesthesia and mechanical ventilation, and the $O_2$ uptake increased during the same period. Due to this divergence of values for $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ during anesthesia there was a progressive decrease in the calculated ratio for respiratory gas exchange ($R_E$). For most cases the $R_E$ decreased to a level of approximately 0.5 during 1 to 2 hours of anesthesia but values as low as 0.35 were not unusual.

The decreased $\dot{V}_{CO_2}$ during anesthesia was observed with few exceptions in the more than 200 patients we studied who were paralyzed with muscle relaxant drugs and mechanically ventilated. $\dot{V}_{CO_2}$ did not decrease in two patients with $N_2O$-$O_2$-tubocurarine anesthesia with no narcotic for premedication or for maintenance of anesthesia and in the few patients we studied with spontaneous ventilation during anesthesia; one of these is included in the following case reports. $\dot{V}_{O_2}$ was also measured in 27 of the 200 patients. $\dot{V}_{O_2}$ consistently rose throughout the surgical procedure as long as blood pressure was maintained. Data obtained from these few cases indicate that $O_2$ consumption may be more sensitive to transient decreases in blood pressure than is $CO_2$ excretion.

The rate of decrease of $\dot{V}_{CO_2}$ in a specific patient is necessarily proportional to the minute volume of ventilation. It is apparent from the data given in Table 2 that there was variation in the minute volume of ventilation from patient to patient and the case reports show that there was variation in the minute volume of each patient during the surgery. The variations in minute volume noted in an individual patient with time are due to changes in patient pulmonary compliance relating to depth of anesthesia and muscular relaxation and to extraneous factors such as changes in position, retraction and packing, and surgeons' elbows. In 10 patients chosen randomly from the study group with mean minute volumes varying from 3.4 to 5.5 L/min the differences in 15-minute interval measurements of $\dot{V}_{CO_2}$ varied from 1.1% to 3.2% of the mean. Analysis of the relation between $\dot{V}_{CO_2}$ and the minute volume of ventilation is not meaningful for this small number of patients with so few samples from each one. For many but not most of the patients studied to date there is good correlation ($r = 0.80$ or better) for the variation of $\dot{V}_{CO_2}$ and minute volume. With on-line computation a more comprehensive and better controlled study of this relation will be possible.

**TABLE 1**
**$CO_2$ Excretion during General Anesthesia and Surgery***

| | Anesthesia duration (min) | | | | |
|---|---|---|---|---|---|
| | 15 | 30 | 45 | 60 | 75 |
| | | | *ml/min* | | |
| Total $CO_2$ excretion | 173 | 163 | 155 | 148 | 143 |
| (n = 50) | ±39 | ±32 | ±30 | ±33 | ±31 |
| $CO_2$ excretion $m^2$ BSA | 104 | 98 | 91 | 90 | 87 |
| (n = 50) | ±23 | ±19 | ±22 | ±21 | ±20 |

* Values shown are means ± SD.

## Case Reports

Tables 3 and 4 show data from one case with uncomplicated anesthesia and surgery and from two cases in which there was considerable blood loss. The two cases presented in Table 3 were done on the same day with the same anesthesia equipment and were women of comparable height and weight. Patient 2 was older and had a diagnosis of ovarian carcinoma. Surgery was complicated by blood loss of 1500 ml which was replaced as it occurred. At no

**TABLE 2**

**$CO_2$ Excretion and $O_2$ Consumption (ml/min) during General Anesthesia**

| Case | Age | BSA | Vent Vol Mean | $CO_2$ Anesthesia duration (min) | | | | | $O_2$ Anesthesia duration (min) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 15 | 30 | 45 | 60 | 75 | 15 | 30 | 45 | 60 | 75 |
| | *yr* | *m²* | *L/min* | | | | | | | | | | |
| 1 | 52 | 1.64 | 6.54 | 209 | 198 | 171 | 175 | 166 | 250 | 263 | 272 | 275 | 267 |
| 2 | 28 | 1.89 | 5.29 | 193 | 198 | 173 | 176 | 157 | 187 | 181 | 191 | 209 | 206 |
| 3 | 44 | 1.72 | 5.43 | 171 | 158 | 129 | 129 | 135 | — | 159 | 164 | 168 | 169 |
| 4 | 39 | 1.58 | 4.95 | 134 | 126 | 116 | 104 | 98 | 161 | 161 | 156 | 196 | 211 |
| 5 | 42 | 2.00 | 5.04 | 118 | 128 | 133 | 109 | 103 | 96 | 106 | 148 | 142 | 140 |
| 6 | 36 | 1.67 | 6.49 | 174 | 161 | 154 | 149 | 152 | 177 | 177 | 178 | 152 | 203 |
| 7 | 28 | 1.67 | 4.10 | 155 | 148 | 136 | 132 | 126 | — | 186 | 216 | 211 | 220 |
| 8 | 44 | 1.70 | 5.05 | 114 | 117 | 114 | 110 | 104 | 202 | 223 | 251 | 257 | 259 |
| 9 | 53 | 1.82 | 5.27 | 141 | 116 | 134 | 131 | 138 | 214 | 186 | 222 | 218 | 240 |
| 10 | 28 | 1.50 | 4.62 | 153 | 168 | 165 | 168 | 159 | 161 | 158 | 165 | 171 | 167 |
| 11 | 52 | 1.67 | 6.91 | 253 | 229 | 215 | 211 | 205 | 192 | 205 | 213 | 209 | 200 |
| 12 | 36 | 1.52 | 5.75 | 212 | 207 | 190 | 201 | 204 | 192 | 198 | 187 | 217 | 210 |
| Mean | | | | 168.9 | 162.8 | 152.5 | 149.6 | 145.6 | 183.2 | 183.6 | 196.9 | 202.1 | 207.7 |
| SD | | | | ±41.8 | ±38.1 | ±31.0 | ±36.3 | ±35.8 | ±40.2 | ±38.6 | ±38.7 | ±39.6 | ±37.1 |

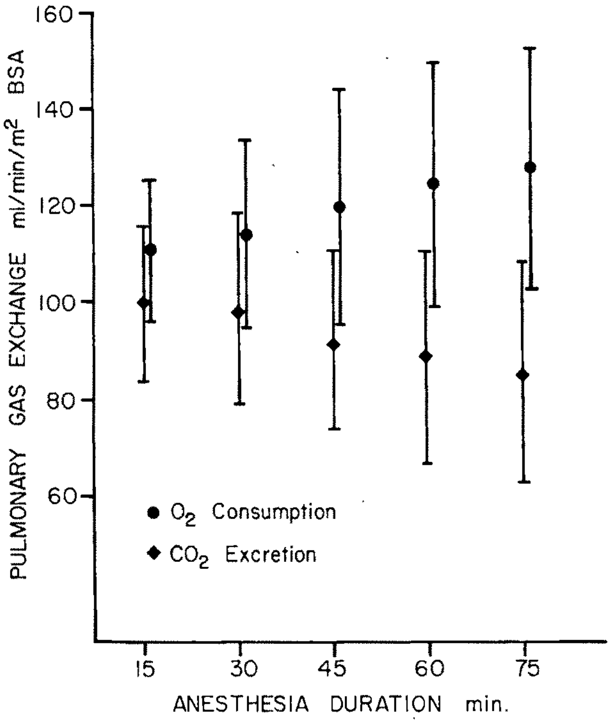


FIGURE. $CO_2$ excretion and $O_2$ consumption during general anesthesia and mechanical ventilation for lower abdominal surgery. Points represent the mean and standard deviation for values per square meter of body surface area from 12 normal women.

time in this case or in the case presented in Table 4 was the systolic blood pressure less than 100 mm Hg.

Patient 1 in Table 3 shows the increase in $\dot{V}_{O_2}$ and the decrease in $\dot{V}_{CO_2}$ seen in most patients under general anesthesia. Though the volume of ventilation was not excessive (500 ml tidal volume, rate 10/min), the maximal alveolar $P_{CO_2}$, which we find is very close to arterial $P_{CO_2}$ in normal patients even under anesthesia, decreased from 28 to 20 mm Hg. These values are similar to those observed in the patient 2 (Table 3) until blood loss became excessive at the end of the 1st hour of anesthesia. $\dot{V}_{CO_2}$ appears not to have been affected but $\dot{V}_{O_2}$ decreased when increased blood loss began even though blood pressure remained unchanged.

The patient whose data are shown in Table 4 was a 63-year-old woman in the lateral position for placement of total hip prostheses. Preoperative hemoglobin level was 8 g % and she was transfused from the time of endotracheal intubation. $\dot{V}_{O_2}$ was low in this patient from the first measurement at 21 minutes after intubation; it did not increase in the 1st hour and then decreased to very low levels as surgery progressed. Methyl methacrylate was used during the period preceding each of the last two measurements (180 and 225 minutes after intubation). Ventilation was spontaneous throughout this case and $\dot{V}_{CO_2}$ and alveolar $P_{CO_2}$ remained at or near the postinduction levels.

## Discussion

The simultaneous measurement of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ measures pulmonary gas exchange and this is essentially the measurement of the effective pulmonary blood flow, the pulmonary perfusion that is exposed to gas exchange. In the absence of measurements of cardiac output, noninvasive measurements showing normal levels of $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ indicate that cardiac output and pulmonary blood flow are adequate for basal needs. $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ may be used to calculate cardiac output in the Fick equation if arterial and mixed venous blood samples are available; values for both gas exchange and arteriovenous difference must be measured, not estimated from other values or assumed, if cardiac output is measured.

An increase or decrease in $P_{CO_2}$ of both expired gas and blood may be associated with a similar change in

**TABLE 3**
**Pulmonary Gas Exchange during Anesthesia and Hysterectomy**

| Patient no | Time after intubation | Vent vol | $\dot{V}_{CO_2}$ | $\dot{V}_{O_2}$ | Alveolar $P_{CO_2}$ | Arterial blood pressure | Heart rate |
|---|---|---|---|---|---|---|---|
| | *min* | *ml* | *ml/min* | *ml/min* | *mm Hg* | *mm Hg* | *beats/min* |
| 1* | 11 | 5110 | 134 | 161 | 28 | 98/75 | 77 |
| | 21 | 5096 | 126 | 161 | 26 | 110/70 | 66 |
| | 36 | 5134 | 116 | 156 | 24 | 110/65 | 64 |
| | 51 | 5026 | 104 | 196 | 23 | 104/70 | 64 |
| | 66 | 5134 | 98 | 211 | 22 | 110/70 | 66 |
| | 81 | 4841 | 68 | 210 | 19 | 86/58 | 67 |
| | 96 | 5193 | 79 | 269 | 21 | 100/65 | 65 |
| | 111 | 4859 | 66 | 260 | 20 | 94/65 | 67 |
| 2† | 13 | 4829 | 127 | 146 | 30 | 86/50 | 64 |
| | 17 | 4826 | 122 | 150 | 29 | 114/70 | 81 |
| | 24 | 4838 | 121 | 152 | 30 | 140/75 | 78 |
| | 43 | 4720 | 80 | 164 | 21 | 140/85 | 78 |
| | 59 | 4791 | 66 | 170 | 18 | 124/70 | 74 |
| | 90‡ | 4823 | 78 | 142 | 21 | 124/80 | 74 |
| | 99 | 4805 | 91 | 154 | 23 | 94/70 | 75 |
| | 117 | 5067 | 81 | 145 | 21 | 104/80 | 80 |
| | 147 | 5121 | 79 | 118 | 19 | 110/80 | 77 |

* Patient 1 (no 126): height, 160 cm; weight 56.5 kg; age, 39 years; premedication, morphine sulfate (10 mg), hydroxyzine-HCl (25 mg), and glycopyrrolate (0.2 mg); anesthesia, $N_2O$-$O_2$-fentanyl, tubocurarine; ventilation, mechanical ventilator.

† Patient 2 (no 127): height, 159 cm; weight 56.5 kg; age, 62 years; premedication, morphine sulfate (8 mg), hydroxyzine-HCl (25 mg), glycopyrrolate (0.2 mg); anesthesia, $N_2O$-$O_2$-fentanyl, tubocurarine; ventilation, mechanical ventilator.

‡ Blood loss: 1500 ml, replaced with three units of transfused blood.

**TABLE 4**
**Pulmonary Gas Exchange during General Anesthesia and Total Hip Replacement***

| Time after intubation | Vent vol | $\dot{V}_{CO_2}$ | $\dot{V}_{O_2}$ | Alveolar $P_{CO_2}$ | Arterial blood pressure | Heart rate | Central venous pressure |
|---|---|---|---|---|---|---|---|
| *min* | *ml* | *ml/min* | *ml/min* | *mm Hg* | *mm Hg* | *beats/min* | *cm $H_2O$* |
| 21† | 3167 | 160 | 130 | 39 | 122/68 | 85 | 13 |
| 45 | 3958 | 183 | 153 | 38 | 136/73 | 80 | 14 |
| 61 | 3929 | 187 | 163 | 38 | 124/68 | 76 | 8 |
| 75‡ | 2929 | 150 | 130 | 41 | 130/68 | 84 | 8 |
| 105 | 3614 | 174 | 140 | 39 | 120/68 | 81 | 7 |
| 150 | 5120 | 160 | 115 | 39 | 104/61 | 79 | 5 |
| 180 | 3546 | 147 | 77 | 35 | 109/66 | 78 | 12 |
| 225 | 3771 | 169 | 101 | 38 | 103/66 | 71 | 6 |

* Patient (no 139): height, 163 cm; weight, 49 kg; age, 63 years; premedication, none; anesthesia, $N_2O$-$O_2$-enflurane; ventilation, spontaneous.

† Arterial blood: pH 7.37, $P_{CO_2}$, 42 mm Hg; $P_{O_2}$, 95 mm Hg.

‡ Estimated blood loss: 2500 ml. Blood replaced intraoperatively, 3½ unit lactated Ringer's solution, 1000 ml, normal saline, 1500 ml

$\dot{V}_{CO_2}$ but there is not a direct relationship. A change in ventilatory volume produces an immediate effect on expired and blood $P_{CO_2}$ and may change $\dot{V}_{CO_2}$ temporarily but total $\dot{V}_{CO_2}$ is still determined mainly by body production, the systemic circulation, and mechanisms of $CO_2$ transport. During anesthesia with mechanical ventilation $\dot{V}_{CO_2}$ usually decreases progressively with a relatively small change in arterial and expired $P_{CO_2}$. We know from both clinical studies and as yet unpublished animal experiments that this is possible because the venoarterial $CO_2$ difference decreases; the amount of $CO_2$ released in the lungs by a specific volume of blood flow is less. Arteriovenous $O_2$ difference can also vary as $O_2$ consumption changes to meet body needs or circulation is altered, as may occur with the increased cardiac perfusion and limited tissue perfusion of septic shock.[2]

The validity of the Fick calculation for cardiac output using measured values for pulmonary gas exchange and blood gas contents during clinical anesthesia must still be investigated. However, we found very good correlation (r = 0.86) in dogs when the direct Fick measurement of cardiac output using $\dot{V}_{CO_2}$ from our method was compared with dye dilution cardiac output determinations during pentobarbital-tubocurarine anesthesia.

Although the ventilatory tidal and minute volumes used for the patients in this study were moderate, the corresponding decrease in $P_{CO_2}$ indicates that they were overventilated. This observation is supported by the fact that the few cases we studied with spontaneous ventilation did not have a comparable decreased $P_{CO_2}$ and $CO_2$ output. There is also evidence that the more heavily narcotized patients may have less $CO_2$ output because the few patients we studied without narcotic premedication or maintenance during anesthesia had higher $CO_2$ outputs. The metabolic acidosis due to narcotic depression and anesthesia could be a significant factor which is masked by the concurrent respiratory alkalosis. The decreased body temperature during surgery and mechanical ventilation and the volume and type of infused fluids are pertinent factors. The extent of renal bicarbonate excretion is also relevant to the study of $CO_2$ balance during anesthesia.

The concurrent increase in $O_2$ uptake implies that reduced basal metabolism is not one cause for the decreased $\dot{V}_{CO_2}$, but there are other factors which can increase the $O_2$ uptake. A lighter stage of anesthesia due to decreasing fentanyl effect increases $\dot{V}_{O_2}$ in some patients but this is often modified by the decreased surgical stimulation at the end of the case. Theye, Gronert, and Heffron[3] demonstrated an increase in $\dot{V}_{O_2}$ with hypocapnic alkalosis in hyperventilated dogs. Patterson and Sullivan[4] also showed increased $\dot{V}_{O_2}$ with respiratory alkalosis and the effect was enhanced by sodium bicarbonate infusion. Most of our patients received a liter of lactated Ringer's solution during the 1st hour of the case. Preliminary work to evaluate the effect of either intravenous lactated Ringer's solution or normal saline on $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ is as yet inconclusive.

We have found no reports in the literature that give sequential values for pulmonary gas exchange during extended periods of anesthesia with mechanical ventilation under clinical conditions. Bain and Spoerel[5] obtained a mean value of 92 ± 13 ml/$m^2$ BSA/min for $\dot{V}_{CO_2}$, 1 hour after induction of anesthesia in 17 adult male and female patients during $N_2O$-$O_2$-alphaprodine anesthesia with controlled ventilation. Our comparable value in 50 women was 89.8 ± 21 ml/$m^2$ BSA/min. Christensen[6] found in seven patients during $N_2O$-narcotic anesthesia $\dot{V}_{CO_2}$ was 184 ml/min STPD. Our mean value for 50 women 15 minutes after intubation was 157 ml/min STPD, considerably lower but Christensen does not give sex, height, weight, or premedication in his small number of patients. Nunn, Bergman, and Coleman[7] found mean $\dot{V}_{O_2}$ to be 215 ml/min and $\dot{V}_{CO_2}$ 180 ml/min in 17 patients of both sexes during $N_2O$-$O_2$-meperidine anesthesia and mechanical ventilation. The duration of anesthesia was less than 50 minutes for most of their patients, but the authors observed that the $R_E$ and $CO_2$ output tended to decrease during the 1st hour of anesthesia. Westenskow and Jordan[8] measured $\dot{V}_{O_2}$ in 17 patients with mechanical ventilation during balanced anesthesia and found mean $\dot{V}_{O_2}$ in 24 measurements made at unspecified times during anesthesia to be 239.7 ± 50 ml/min.

Theye and Tuohy[9] measured $\dot{V}_{O_2}$ during controlled respiration with halothane anesthesia maintained at the lowest concentration that would ensure freedom from movement. In the absence of premedication and without thiopental, average $\dot{V}_{O_2}$ was 100% of predicted conscious basal values with a range of 80 to 120% in 10 patients. With premedication and thiopental $\dot{V}_{O_2}$ averaged 84% of predicted values but increased with time. In seven patients who received no premedication or thiopental but were paralyzed with either tubocurarine or succinylcholine intravenous drip $\dot{V}_{O_2}$ was also 84% of basal predicted values.

Data for $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ from these reports are difficult to compare with each other and with our data because methods of measurement, measuring times, the types of anesthesia, and premedication were not controlled. But the results indicate that the type of anesthesia, the types of adjunctive drugs used and the combinations in which they were used, and particularly the effect of mechanical ventilation are major factors in determining $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during anesthesia.

In conclusion, this report describes a noninvasive computer-asisted monitoring system for $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during anesthesia and presents preliminary data from clinical patients to illustrate its use. $\dot{V}_{O_2}$ progressively increases during anesthesia and surgery; $\dot{V}_{CO_2}$ decreases, though not necessarily simultaneously with increases in $\dot{V}_{O_2}$. Decreases in $\dot{V}_{O_2}$ are observed with moderate lowering of blood pressure before changes in $\dot{V}_{CO_2}$ become apparent; the clinical significance of this observation requires further investigation.

## REFERENCES

1. Noe FE: Computer analysis of curves from an infrared $CO_2$ analyzer and screen-type airflow meter. J Appl Physiol 18:149–157, 1963
2. Gump FE, Kinney JM, Price JB: Energy metabolism in surgical patients: oxygen consumption and blood flow. J Surg Res 10: 613–627, 1970
3. Theye RA, Gronert GA, Heffron JAH: Oxygen uptake of canine whole body and hind limb with hypocapnic alkalosis. Anesthesiology 47:416–422, 1977
4. Patterson RW, Sullivan SF: Determinants of oxygen uptake during sodium bicarbonate infusion. J Appl Physiol 45:399–402, 1978
5. Bain JA, Spoerel WE: Carbon dioxide output in anaesthesia. Can Anaesth Soc J 23:153–162, 1976
6. Christensen KN: A simple method of monitoring carbon dioxide in anaesthetized patients. Acta Anaesthesiol Scand 21:314–319, 1977
7. Nunn JF, Bergman NA, Coleman AJ: Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. Br J Anaesth 37:898–914, 1965
8. Westenskow DR, Jordan WS: Changes in oxygen consumption induced by fentanyl and thiopentone during balanced anaesthesia. Can Anaesth Soc J 25:18–21, 1978
9. Theye RA, Tuohy GF: Oxygen uptake during light halothane anesthesia in man. Anesthesiology 25:627–633, 1964

---

## Treatment of Lobar Atelectasis

To evaluate the usefulness of fiberoptic bronchoscopy for treatment of acute lobar atelectasis, 31 subjects were randomly assigned to treatment by fiberoptic bronchoscopy followed by respiratory therapy for 48 hours, or to respiratory therapy alone for the same period. Respiratory therapy included lung hyperinflation, coughing or tracheal suctioning, bronchodilator inhalation, and chest percussion with postural drainage, at 4-hour intervals. No significant differences between groups with regard to restoration of volume loss were detected after the first treatment, after 24 hours, or after 48 hours ($p > 0.20$). The mean percentage resolution of volume loss immediately after bronchoscopy (38%) closely approximated that after the first respiratory therapy treatment in subjects who had not undergone bronchoscopy (37%). An air bronchogram proved to be a predictor of delayed resolution for both groups. At 24 hours, 26% of the initial volume loss was recovered in 11 subjects with air bronchograms, whereas 20 subjects without air bronchograms demonstrated 83% resolution ($p < 0.001$). These results suggest that fiberoptic bronchoscopy does not add to respiratory therapy in the treatment of acute lobar atelectasis and that an air bronchogram predicts delayed resolution of collapse. *(Marini JJ, Pierson DJ, Hudson LD: Acute lobar atelectasis: A prospective comparison of fiberoptic bronchoscopy and respiratory therapy. Am Rev Respir Dis 119:971–978, 1979)*

ANESTH ANALG
59:270-274, 1980

# Resistance to Breathing in Healthy Subjects following Endotracheal Intubation under Topical Anesthesia

**Thomas J. Gal, MD,* and Paul M. Suratt, MD†**

---

GAL, T. J., AND SURATT, P. M.: Resistance to breathing in healthy subjects following endotracheal intubation under topical anesthesia. Anesth Analg 59:270–274, 1980.

To identify possible airway constriction following endotracheal intubation under topical anesthesia, airway resistance (Raw) and specific conductance (sGaw) were measured with a body plethysmograph in six awake, healthy, nonsmoking men aged 23 to 29. Subjects were studied while breathing under four conditions: (1) through a large bore mouthpiece (control); (2) through an 8.0-mm internal diameter 25-cm long endotracheal tube held externally (external resistance); (3) while intubated with an identical endotracheal tube; and (4) following extubation as they again breathed through the mouthpiece. To determine the effect of the lidocaine aerosol used for topical anesthesia prior to intubation, Raw was measured in six additional subjects before and after the upper airway had been topically anesthetized. Topical anesthesia produced no significant change in Raw or sGaw in these subjects. In subjects whose tracheas were intubated the mean values of Raw (in cm $H_2O$/L/sec) and sGaw (in L/sec/cm $H_2O$/L) in each of the four above conditions were: control, 0.99, 0.30; external resistance, 2.34, 0.13; intubation, 2.75, 0.11; and following extubation, 1.00 and 0.30. The increase in Raw and decrease in sGaw during tracheal intubation were significantly greater than the changes noted with subjects breathing through the tube as an external resistance ($p < 0.01$). Tracheal intubation increased residual volume and decreased vital capacity but did not alter functional residual capacity or total lung capacity. We conclude that tracheal intubation under topical anesthesia increases airway resistance more than the resistance produced by the addition of the tube to the control airway. This additional resistance reflects reflex narrowing of airways distal to the tube, which may be more severe in patients whose airways are not anesthetized.

**Key Words:** AIRWAY, Resistance; INTUBATION, Endotracheal: airway resistance.

---

ENDOTRACHEAL intubation imposes a mechanical burden on spontaneously breathing patients in the form of a fixed upper airway resistance.[1] Previous work suggests that the fixed resistance of the tube merely substitutes for the resistance of the upper airway.[2] However, our recent work strongly suggests that tracheal intubation also affects the airways distal to the tube since forced expiratory flows below mid vital capacity are reduced following intubation in awake subjects.[3] These changes suggest the likelihood of constriction in the peripheral airways which may further increase the work of breathing and impair gas exchange in patients whose tracheas are intubated. However, no direct measurements of airway resistance (Raw) have been made to identify constriction in these airways.

The purpose of the present study was to determine whether endotracheal intubation increases resistance

---

* Assistant Professor, Anesthesiology.

† Assistant Professor, Internal Medicine.

Supported in part by funds from the American Lung Association.

Received from the Department of Anesthesiology and the Pulmonary Division, Department of Internal Medicine, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication December 12, 1979. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Chicago, Illinois, October 1978.

Reprint requests to Dr. Gal, Box 238, Department of Anesthesiology, University of Virginia Medical Center.

in the airways distal to the tube. We, therefore, measured Raw in subjects during normal breathing, during breathing through an externally held endotracheal tube, and while intubated. We assumed that if the Raw of subjects who were intubated exceeded the sum of their control Raw plus the resistance added by the endotracheal tube this would indicate increased resistance and therefore constriction in airways distal to the tube.

## Methods and Materials

Six healthy male volunteers aged 23 to 29 served as subjects. All were nonsmokers with neither history nor symptoms of respiratory disease. The project was approved by the Human Studies Committee and informed consent was obtained from each subject. Physiologic measurements were performed with subjects in the sitting position. All subjects were tested under four conditions: (1) while breathing through a 25-mm i.d. mouthpiece (control); (2) while breathing through an externally held 8.0-mm i.d. 25-cm long endotracheal tube (external resistance); (3) after intubation with an identical 8.0-mm endotracheal tube; (4) 10 minutes after extubation. Eight to 10 ml of 4% lidocaine administered by an ultrasonic nebulizer (Mistogen) provided topical anesthesia of the airway. This was supplemented by occasional sprays of the same solution to the upper airway during laryngoscopy. The tube was inserted orally to its full depth just above the carina and the cuff was inflated to produce a leak-free seal. This was assured by instructing subjects to inspire to near total lung capacity and then relax against an occluded mouthpiece. Airway pressure sensed by an aneroid monometer held constant for 5 seconds indicated that the seal was adequate. Vital capacity measurements and auscultation of the chest ensured that intubation was not endobronchial. When held externally for all measurements, the tube was curved to simulate its shape in the intubated subjects.

Airway resistance (Raw) was measured by the method of Dubois, Botelho and Comroe[4] using a variable pressure, constant volume body plethysmograph. Raw measured at functional residual capacity (FRC) during panting at flows of 0.5 L/sec was converted to its reciprocal airway conductance (Gaw), which is directly related to lung volume in a linear fashion. In order to eliminate changes produced by variations in lung volume, Gaw was expressed as specific conductance (sGaw) by dividing Gaw by FRC. The FRC was measured by having subjects pant against a closed shutter at the end of a normal expiration. The mean values from 10 satisfactory measurements of Raw and FRC were used. Total lung capacity (TLC) was calculated by adding inspiratory capacity (IC) from spirometry to FRC obtained plethysmographically. Residual volume (RV) was calculated by subtracting the largest value for vital capacity from TLC. Vital capacity (VC) and its subdivisions were measured with a waterless rolling seal spirometer (Ohio Medical Products model 840) following each set of plethysmographic studies. Subjects performed at least three vital capacity meneuvers during each testing condition, and the largest value was used. Electrocardiograms were monitored continuously in all subjects and blood pressure measured periodically.

The sequence of measurements began with the control period followed by subjects breathing through the externally held endotracheal tube (external resistance). Next the subjects inhaled the lidocaine aerosol through a mouthpiece for 10 minutes, at which point pharyngeal numbness and difficulty swallowing were noted. The endotracheal tube was inserted orally by direct laryngoscopy within 10 minutes of achieving this topical anesthesia. Following a 5-minute period of "acclimatization" to the tube, subjects entered the plethysmograph. Measurements after intubation were made 10 to 15 minutes following removal of the tube while the subjects again breathed through the mouthpiece.

To determine the possible effect of the lidocaine aerosol on airway resistance in subjects whose tracheas were intubated, airway resistance was also measured in six additional healthy subjects before and after inhalation of 8 to 10 ml of 4% lidocaine administered by an ultrasonic nebulizer. These subjects thus received topical anesthesia of the airway but their tracheas were not intubated.

The data were analyzed using Student's *t*-test for paired observations and are presented as means ± standard error of the mean (SEM).

## Results

Baseline pulmonary function tests for the six healthy subjects are listed on Table 1 and indicate that the conventional spirometric indices (FVC, $FEV_1$) for the most part exceeded predicted values.[5] Control Raw (0.93 ± 0.09 SEM cm $H_2O$/L/sec increased to 2.34 ± 0.08 SEM (Fig 1) when subjects breathed through the external resistance. The increase in Raw imposed by the external endotracheal tube ranged between 1.2 and 1.5 cm $H_2O$/L/sec. Following tra-

**TABLE 1**

**Baseline Pulmonary Function in Six Normal Subjects***

| Subject | Age | Height | FVC | $FEV_1$ | $FEV_1$/FVC | Raw | sGaw |
|---|---|---|---|---|---|---|---|
| | *yr* | *cm* | *L* | *L* | % | *cm $H_2O$/L/sec* | *L/sec/cm $H_2O$/L* |
| 1 | 25 | 178 | 5.90 (107) | 4.90 (101) | 83 | 1.06 | 0.31 |
| 2 | 24 | 188 | 7.50 (123) | 5.80 (121) | 76 | 1.40 | 0.22 |
| 3 | 25 | 188 | 5.80 (95) | 4.90 (103) | 84 | 0.80 | 0.39 |
| 4 | 29 | 180 | 6.40 (115) | 5.00 (115) | 78 | 1.03 | 0.26 |
| 5 | 23 | 188 | 6.40 (104) | 5.20 (108) | 83 | 0.75 | 0.31 |
| 6 | 28 | 180 | 6.40 (115) | 5.60 (128) | 83 | 0.95 | 0.32 |
| Mean | 25.6 | 184 | 6.40 | 5.20 | 81 | 0.99 | 0.30 |
| SEM | 0.9 | 1.9 | 0.24 | 0.15 | 1.3 | 0.09 | 0.02 |

* Abbreviations used are: FVC, forced vital capacity; $FEV_1$, 1 second forced expiratory volume; $FEV_1$/FVC%, forced expiratory volume in 1 second expressed as percentage of forced vital capacity; Raw, airway resistance measured at 0.5 L/sec; sGaw, specific conductance, the reciprocal of airway resistance divided by functional residual capacity. Values in parentheses indicate percent of predicted value (Morris and associates[5]).

cheal intubation all subjects demonstrated further increase in Raw to 2.75 ± 0.10 SEM cm $H_2O$/L/sec. Paired *t*-test indicated that this value was significantly greater than the Raw with the external resistance ($p < 0.01$). Changes in sGaw were in accord with these findings. Control sGaw (0.30 ± 0.02 SEM) decreased to 0.13 ± 0.02 SEM with the external resistance. During tracheal intubation sGaw (0.11 ± 0.01 SEM) was significantly less than the external resistance ($p < 0.01$). Following extubation both Raw and sGaw returned to control levels. The mean resistance of the tube, calculated by subtracting control Raw from that measured when the subjects breathed through the externally held tube, was 1.35 cm $H_2O$/L/sec. At 0.5 L/sec the resistance of the airways distal to the tube in the subjects who were intubated was calculated by subtracting tube resistance from total Raw. This mean value was 1.40 cm $H_2O$/L/sec.

Changes in lung volumes during the four experimental conditions are listed in Table 2. FRC increased slightly in three intubated subjects, decreased slightly in two, and was unchanged in the remaining subject. The mean value of 3.46 L did not differ significantly from control. Values for IC and TLC likewise did not vary significantly from control during any of the other conditions. However VC decreased and RV increased significantly both after tracheal intubation and following extubation ($p < 0.05$).

Although insertion of the endotracheal tube provoked mild coughing, subjects had no subsequent discomfort after the tube was in place. Blood pressures and heart rates did not vary significantly from the control levels. Pharyngeal numbness began to subside by the end of the plethysmographic measurements in most subjects. Burning and irritation in the chest and lower neck area were frequently experienced during the vital capacity maneuvers which followed.

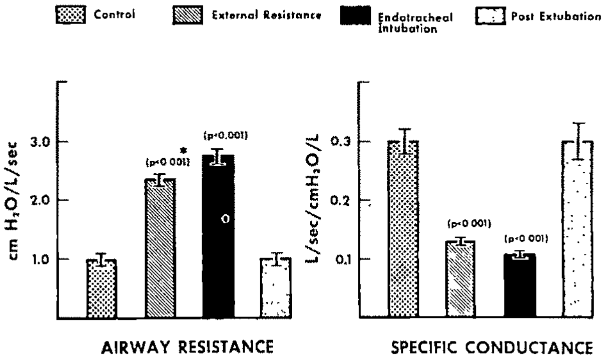


FIG 1. Airway resistance and specific conductance during the four experimental conditions. Data obtained from six subjects are plotted as mean values. Bars represent ± SEM. * Values in parentheses give degree of statistical significance when compared to control by paired *t*-test. Measurements during endotracheal intubation differed significantly from the external resistance ($p < 0.01$) when compared by paired *t*-test.

In the six subjects who received only lidocaine aerosol, mild coughing occurred following the initial breath of the mist. Following the aerosol treatment they demonstrated the same symptoms of pharyngeal numbness, difficulty in swallowing and vocal paresis noted by subjects who were lated intubated.

Control Raw (1.21 ± 0.1 SEM) decreased to 1.08 ± 0.1 following the lidocaine aerosol (Fig 2), but this change was not significant. Changes in sGaw were also not statistically significant.

## Discussion

This study indicates that Raw in healthy subjects whose tracheas are intubated under topical anesthesia

**TABLE 2**

**Lung Volume Measurements during the Four Experimental Conditions***

| | Control | External resistance | Endotracheal intubation | After extubation |
|---|---|---|---|---|
| Functional residual capacity (L) | 3.47 ± 0.21 | 3.55 ± 0.17 | 3.46 ± 0.15 | 3.50 ± 0.18 |
| Inspiratory capacity (L) | 4.13 ± 0.22 | 4.15 ± 0.28 | 4.00 ± 0.21 | 4.18 ± 0.20 |
| Total lung capacity (L) | 7.62 ± 0.27 | 7.70 ± 0.30 | 7.47 ± 0.25 | 7.67 ± 0.18 |
| Residual volume (L) | 1.20 ± 0.18 | 1.35 ± 0.20 | 1.55 ± 0.17† | 1.49 ± 0.15† |
| Vital capacity (L) | 6.38 ± 0.24 | 6.27 ± 0.28 | 5.90 ± 0.28† | 6.18 ± 0.20† |

* Values are means ± SEM.

† $p < 0.05$ denotes significant difference from control by paired *t*-test.

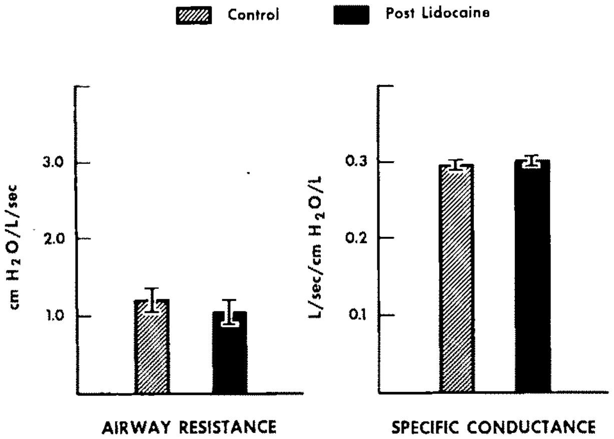


FIG 2. Airway resistance and specific conductance before (control) and after lidocaine aerosol. Data from six subjects are plotted as mean values. Bars represent ± SEM.

exceeds the sum of the resistances of the tube and the control airway. The Raw in the airways distal to the tube in our subjects was calculated as 1.40 cm $H_2O$/L/sec. This value is 141% of control Raw (0.99 cm $H_2O$/L/sec) and thus suggests that tracheal intubation increases resistance in airways distal to the tube. The increase in Raw in airways distal to the tube is even more striking if a truly appropriate comparison of Raw is made. In subjects whose tracheas are intubated the tube bypasses the upper airways which normally account for at least one third of Raw during mouth breathing.[6] This one third represents a value of about 0.33 cm $H_2O$/L/sec in our subjects. Thus, control values for resistance of the airways below the tube would be 0.99 − 0.33 = 0.66 cm $H_2O$/L/sec. In our subjects this value following tracheal intubation was about 1.40 cm $H_2O$/L/sec or 210% of the hypothetical control value.

These conclusions are based upon a mean calculated value of 1.35 cm $H_2O$/L/sec for the resistance of the endotracheal tube. This is similar to that reported by Sahn et al.[1] However, Demers et al[7] have reported that the resistance of an 8-mm endotracheal tube measured in isolation is nearly 3 times this value at a constant flow of 0.5 L/sec (i.e., 3.7 cm $H_2O$/L/sec). This value is clearly not likely in our experimental conditions since the Raw measured with the tube as an external resistance to subjects' control Raw was only 2.35. Furthermore, Raw measured in subjects whose tracheas were intubated (2.75 cm $H_2O$/L/sec) was less than this value for the tube resistance. Assessing the resistance of the tube in isolation by recording a pressure drop during constant flow may overestimate the effective resistance of the tube in vivo because of kinetic energy dissipation at the end of the tube.[8]

FRC did not change significantly in intubated subjects compared to the other experimental conditions. This suggests that the glottis does not play a role in determining FRC in the adult as has been suggested in infants.[9, 10] The ability to inspire fully to TLC was also unaffected by tracheal intubation. Thus the slight though significant decrease in VC was associated with an increased RV. The RV also increased following extubation but was not accompanied by an increase in Raw. The latter may reflect residual small airway obstruction too slight to be detected by changes in Raw.

Although the increased resistance in airways distal to the endotracheal tube most likely results from the presence of the tube, the possible role of the lidocaine used for topical anesthesia must also be considered. Since the aerosol was administered between measurements made with the external resistance and tracheal intubation, it may have affected the latter. The lidocaine could have acted as a primary irritant and increased Raw as has been shown in patients with reactive airways.[11–13] To explore this possibility we administered lidocaine to six additional subjects. Following the lidocaine neither Raw nor sGaw changed significantly. This finding is in accord with studies of another local anesthetic aerosol (bupivacaine) in healthy subjects.[14] Thus lidocaine is not a likely cause of the added Raw observed during intubation. Furthermore, it is possible that lidocaine, by reducing resting airway tone in some subjects, may have attenuated increases in Raw elicited by the presence of the tube in the trachea.

The most likely cause of the greater than expected resistance associated with tracheal intubation is reflex constriction resulting from airway irritation by the tube. The stimulation of airway receptors in the larynx and trachea with afferents in the vagus nerves could have accounted for the uncomfortable sensation noted by subjects as the topical anesthesia of the airway wore off.[15] Vagal stimulation affects intermediate bronchi and to a great extent more peripheral airways as small as 1-mm diameter.[16, 17] Since the latter collectively have a large cross-sectional area, constriction in these airways will not alter measured values for Raw to as great an extent as constriction of the major bronchi. Raw measured during the standard panting maneuver may also be lower than actual Raw during normal quiet breathing in the presence of this lower airway constriction.[18]

The topical anesthesia of the airway would appear to be a significant factor in reducing the bronchoconstrictive response to airway irritation. Lidocaine provided adequate conditions for tracheal intubation and subjects appeared comfortable during measurements in the body plethysmograph. Although similar data are not available, it is reasonable to presume that patients whose airways are not anesthetized, would demonstrate a greater response to tracheal intubation.

Recent observations in patients during general anesthesia support this speculation.[19] In healthy patients pulmonary resistance was increased more than expected from the resistance of the tube, but the true magnitude of the airway response may have been underestimated by substitution of tube resistance measured in isolation for that of the upper airway. Patients with chronic obstructive pulmonary disease showed even greater increased resistance with tracheal intubation, emphasizing their enhanced responsiveness to airway irritation by the tube.

In summary, changes in Raw and sGaw in subjects whose tracheas were intubated were significantly greater than when the subjects breathed through an identical tube held externally. We conclude that these changes represent an increased resistance in the airways distal to the tube. Although we cannot exclude factors such as psychogenic bronchoconstriction, the most likely cause of this increased resistance is reflex airway constriction involving vagal pathways.[20] Since these effects were observed in subjects whose airways were substantially anesthetized, it is reasonable to speculate that the airway responses would be greater in patients whose tracheas are intubated without prior topical anesthesia or during inadequate depths of general anesthesia.

## ACKNOWLEDGMENT

We wish to thank Dr. D. F. Rochester and Dr. R. M. Epstein for their critical review of the manuscript and Ms. Donna Hooe for her invaluable technical assistance.

## REFERENCES

1. Sahn SA, Laksminarayan S, Petty TL: Weaning from mechanical ventilation. JAMA 235:2208–2212, 1976
2. Colgan FJ, Liang JQ, Barrow RE: Non-invasive assessment by capacitance respirometry of respiration before and after extubation. Anesth Analg 54:807–813, 1975
3. Gal TJ: Pulmonary mechanics in normal subjects following endotracheal intubation. Anesthesiology 52:27–35, 1980
4. DuBois AB, Botelho SY, Comroe JH: A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. J Clin Invest 35:327–334, 1956
5. Morris JF, Koski A, Johnson LC: Spirometric standards for healthy non-smoking adults. Am Rev Respir Dis 103:56–67, 1971
6. Ferris BG, Mead J, Opie LH: Partitioning of respiratory flow resistance in man. J Appl Physiol 19:653–658, 1964
7. Demers RR, Sullivan MJ, Palliotta J: Airflow resistance of endotracheal tubes. JAMA 237:1362, 1977
8. Loring SH, Elliott EA, Drazen JM: Kinetic energy loss and convective acceleration in respiratory resistance measurements. Lung 156:33–42, 1979
9. Olinsky A, Bryan AC: Influence of lung inflation on respiratory control in neonates. J Appl Physiol 36:426–429, 1974
10. Berman LS, Fox WW, Raphaely RC, et al: Optimal levels of CPAP for tracheal extubation of newborn infants. J Pediatr 59: 109–112, 1976
11. Weiss EB, Patwardan AV: The response to lidocaine in bronchial asthma. Chest 72:429–438, 1977
12. Howard P, Cayton RM, Brennan SR, et al: Lidocaine aerosol and persistent cough. Br J Dis Chest 71:19–24, 1977
13. Miller WC, Awe R: Effect of nebulized lidocaine on reactive airways. Am Rev Respir Dis 111:739–741, 1975
14. Cross BA, Guz A, Kain SK, et al: The effects of anesthesia of the airway in dog and man: a study of respiratory reflexes, sensations, and lung mechanics. Clin Sci Mol Med 50:439–454, 1976
15. Guz AA: Respiratory sensations in man. Br Med Bull 33:175–177, 1977
16. Nadel JA, Cabezas GA, Austin JHM: In vivo roentgenographic examination of parasympathetic innervation of the small airways. Invest Radiol 6:9–17, 1971
17. Woolcock AJ, Macklem PT, Hogg JC, et al: Effect of vagal stimulation on central and peripheral airways in dogs. J Appl Physiol 26:806–813, 1969
18. Barter CE, Campbell AH: Comparison of airways resistance measurements during panting and quiet breathing. Respiration 30:1–11, 1973
19. Dohi S, Gold MI: Pulmonary mechanics during general anesthesia. The influence of mechanical irritation on the airway. Br J Anaesth 51:205–214, 1979
20. Widdicombe JG, Kent DC, Nadel JA: Mechanism of bronchoconstriction during inhalation of dust. J Appl Physiol 17:613–616, 1962

ANESTH ANALG
59:275-282, 1980

# Myotoxicity of Single and Repeated Injections of Mepivacaine (Carbocaine) in the Rat

**Marc D. Basson, BS,* and Bruce M. Carlson, MD, PhD†**

BASSON, M. D., AND CARLSON, B. M: Myotoxicity of single and repeated injections of mepivacaine (Carbocaine) in the rat. Anesth Analg 59:275-282, 1980.

Young rats received single or repeated injections of 2% mepivacaine (Carbocaine) into the tibialis anterior or extensor digitorum longus muscles. Repeated injections consisted of six injections of the anesthetic (100 $\mu$l per injection into the tibialis anterior' on three different schedules, at intervals of 2½ hours, 24 hours, or 4 days. The muscles that had been given injections were examined histologically for evidence of myotoxicity at 0 to 7 and 20 days after the last injection. Single injection studies showed that mepivacaine is a myotoxic drug, producing a lesion which ultimately results in the degeneration and subsequent regeneration of large amounts of muscle. A similar picture was seen with repeated injections except that greater tissue destruction was noted. Long-term studies following a single injection of mepivacaine showed restoration of the original muscle structure whereas after repeated injections some muscles showed persisting foci of increased interstitial connective tissue. This study shows that in rats 2% mepivacaine is a myotoxic drug, but that the damage it produces is to a large extent restored by the regeneration of new muscle fibers.

**Key Words:** ANESTHETICS, Local: mepivacaine; MUSCLE, Skeletal: local anesthetic toxicity.

THE LOCAL anesthetics currently in clinical use are widely believed to lack local toxic effects.[1] However, students of skeletal muscle regeneration have for some time used bupivacaine (Marcaine) to induce degeneration of skeletal muscle in lower mammals.[2-5] There have been scattered reports of the induction of degenerative changes by other anesthetics.[6-10] Regeneration physiologists have been interested in the ability of local anesthetics to cause muscle degeneration because this provides a technique for the production of a uniform population of myoblasts for studies on the physiology[11] and biochemistry [12] of regenerating muscle. Except for bupivacaine there has been relatively little systematic work documenting the myotoxic effects of single or repeated doses of other local anesthetics. The question of whether these degenerative changes might produce permanent damage to muscle deserves further attention. In this study the myotoxicity of the local anesthetic mepivacaine (Carbocaine) was evaluated in the rat.

## Materials and Methods

Experiments were conducted on 95 male Sprague-Dawley rats (Charles River). In preliminary experiments involving the extensor digitorum longus (EDL) muscle 25 1-month old rats (80 to 100 g each) were used. In experiments involving single and repeated injections the tibialis anterior muscles of 69 rats (150 to 200 g each) were used. The local anesthetic employed in these experiments was a commercially supplied 2% solution of mepivacaine hydrochloride (Carbocaine, Winthrop). The solutions were injected through standard 25-gauge needles. Each EDL muscle in three rats was penetrated once by the needle alone

---

* Medical Student.

† Professor of Anatomy and Biological Sciences.

Supported by grants from the National Institutes of Health and the Muscular Dystrophy Association.

Received from the Department of Anatomy, University of Michigan, Ann Arbor, Michigan 48109. Accepted for publication December 24, 1979.

Reprint requests to Dr. Carlson.

as a control for possible effects of mechanical trauma alone.

In a preliminary series, one EDL muscle in 15 rats (anesthetized with ether) was surgically exposed and 50 μl of the anesthetic was injected once along its longitudinal axis. The contralateral muscle in each rat was given an injection of 0.9% saline as a control. Muscles were removed for histologic examination 1½,‡ 3 (seven rats), 4 (three rats), 5, 7, 8, and 9 days after injection. Observations in the single injection series were clustered around the 3- to 4-day interval because this represents the optimal time for assessing muscle damage and early repair in the rat.

In a final preliminary experiment the EDL muscle was surgically exposed and 50 μl of mepivacaine was introduced around the muscle but not injected into it. On the control side, equivalent treatment with saline was used. The eight experimental muscles were removed and examined at 3 (four rats), 7, 14, and 38 (two rats) days after exposure to the anesthetic agent.

Seven rats were given single percutaneous injections of 100 μl of mepivacaine into one tibialis anterior muscle and an equal amount of the carrying solution (without the anesthetic agent) into the contralateral muscle. One experimental and one control muscle were examined histologically each day from 1 to 7 days after injection.

In the experimental series involving repeated injections into the tibialis anterior muscle, the hypodermic needle was inserted percutaneously into the distal tip of the muscle, pushed upward to the proximal origin of the muscle, and then withdrawn slowly as 100 μl of mepivacaine was injected. Four muscles in two rats were given injections of 1% trypan blue and examined 10 minutes later as a check on the accuracy of the injections.

There were three series in which rats received six injections of mepivacaine according to different schedules. Rats in series A (11 animals) received injections every 2½ hours. Muscles were examined histologically at 1, 2 (three rats), 4 (two rats), 7 (three rats), and 20 (two rats) days after the last injection. Rats in series B (25 animals) were given injections every day for 6 days, and the muscles were examined histologically at 1 hour, 1 (six rats), 2, 3, 4 (four rats), 5, 6, 7 (four rats), and 20 (six rats) days after the last injection. Rats in series C (24 animals) were given injections every 4 days and muscles were fixed and examined histologically at 1 (four rats), 2, 3, 4 (five rats), 5, 6, 7 (four rats), and 20 (six rats) days after the last injection. One rat died during the series of injections.

All rats of series A to C were given injections of anesthetic in one leg while the contralateral tibialis anterior was subjected simultaneously to one of a variety of control procedures including insertion of the needle without injection, injection of 100 μl of isotonic saline, or injection of 100 μl of a NaCl and KCl solution prepared to be identical with the vehicle used for anesthetic carriage. The sterile saline, used clinically for intravenous infusion, had a pH value of 5.4. Both the anesthetic and the prepared vehicle had a pH value of 5.65.

At the time of sacrifice, the tibialis anterior muscles were removed, weighed and, after gross inspection, fixed in Bouin's solution. Cross-sections for histologic examination after staining with hematoxylin-eosin were taken from the proximal third of the muscle to avoid possible scarring due to multiple needle insertions in the distal region to locate the muscle.

## Results

### Single Injections of Mepivacaine

Neither the mechanical trauma of the needle alone (six muscles), the injection of saline (15 muscles), nor the injection vehicle for mepivacaine (seven muscles) resulted in significant damage to the muscle fibers in the control muscles of the single injection series. A typical example of a control muscle is seen in Fig 1. In no case were more than 50 damaged muscle fibers seen in a control muscle. In contrast, both a single injection of mepivacaine directly into the muscle (22 rats) (Fig 2) or infiltration of the anesthetic onto the undamaged surface of the muscle (eight rats) (Fig. 3) produced widespread histologically evident damage. The histologic course of degeneration and regeneration of muscle fibers following a single injection of mepivacaine was similar to that reported in other descriptions of regeneration of skeletal muscle.[13, 14] A summary of the course of events based upon 30 muscles, obtained daily from 1 to 9 and 38 days after a single exposure to the anesthetic, is presented below. At any given time there was little variation between specimens in either the size of the lesion or the histologic stages of degeneration and regeneration within the muscles.

One day after a single injection of 100 μl of mepivacaine into the tibialis anterior muscle the lesions typically occupied about 30% of the cross-sectional

---

‡ Absence of a number in parentheses indicates that muscle from one rat was obtained for histologic examination at the time indicated.

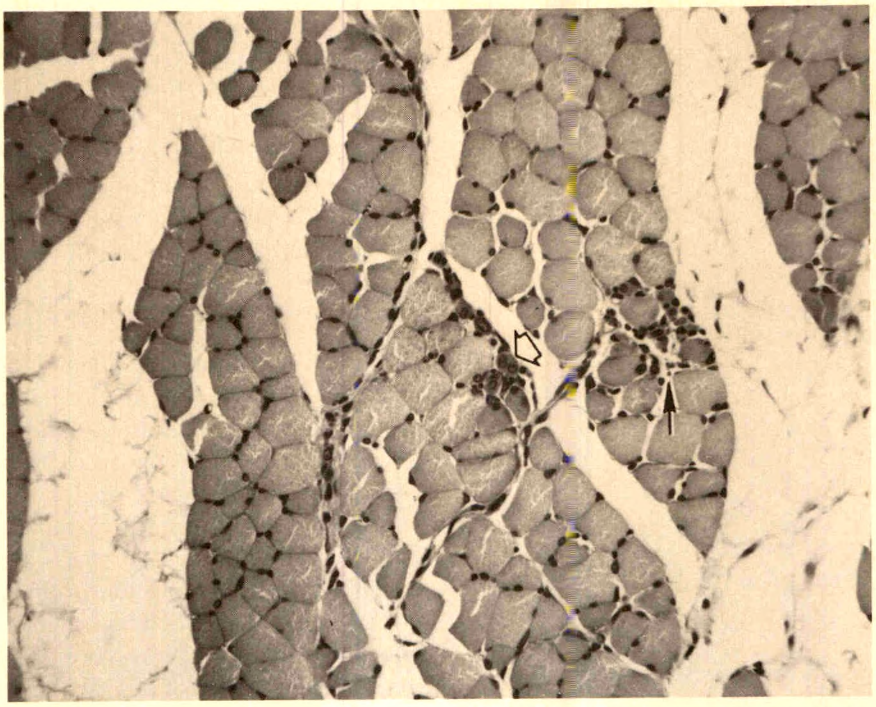


FIG 1. Damaged muscle fibers along the needle track (arrows) 3 days after a single injection of 50 μl of saline into the extensor digitorum longus (EDL) muscle of the rat. Only a small number of muscle fibers have broken down and are regenerating. Hematoxylin-eosin (H&E); 250×.

area of the muscle, although some lesions were considerably smaller. Grossly, the muscles were edematous and reddened. The lesions typically had an ischemic core, with the muscle fibers in this area undergoing limited autolysis. Around this core was a zone of early phagocytic degeneration of damaged muscle fibers. Some degeneration was occasionally seen in restricted areas distant from the main lesion, presumably where the anesthetic leaked from the site of injection along the perimysial fascial planes of the muscle. Over the next 2 days the phagocytic reaction progressed inward from the periphery of the lesion, eliminating the damaged muscle fibers and leaving behind their basement membranes.

In the wake of the phagocytic activity myoblasts lined the persisting basement membranes and the regenerative process began. Regeneration in the core of the lesion continued to lag behind that at the periphery. By the 5th day virtually all muscle fibers in the lesion had degenerated and were replaced by myoblasts, or, in more peripheral areas, by myotubes. In muscles examined at later intervals the myotubes had developed into muscle fibers. With increasing time the diameters of the regenerating muscle fibers attained roughly normal cross-sectional areas. Most of the myonuclei had migrated to peripheral positions, but the persistence of some central nuclei is almost diagnostic of regenerating muscle fibers.

## Repeated Injections

The lesions produced by repeated injections of local anesthetic were significantly larger than those produced by single injections. Lesions associated with repeated injections frequently occupied almost the entire cross-sectional area of the muscle and in no case occupied less than the 30% that was typical of the lesion produced by a single injection. No other gross distinction could be made between muscles subjected to single or repeated injections.

Six injections at intervals of 2½ hours (series A) (11 muscles) produced lesions much like those observed after a single injection (Fig 4). Six injections of 24 hours (series B) (25 muscles) produced a heterogeneous pattern in which myocytes at widely disparate levels of maturity could be seen in each muscle cross-section. Six injections, one every 4 days (series C) (24 muscles) also produced a complicated pattern in which fiber precursors at many different stages of development coexisted in the same muscle, but aggregates of regenerating muscle within individual basement membranes were usually of the same developmental stage (Fig 5).

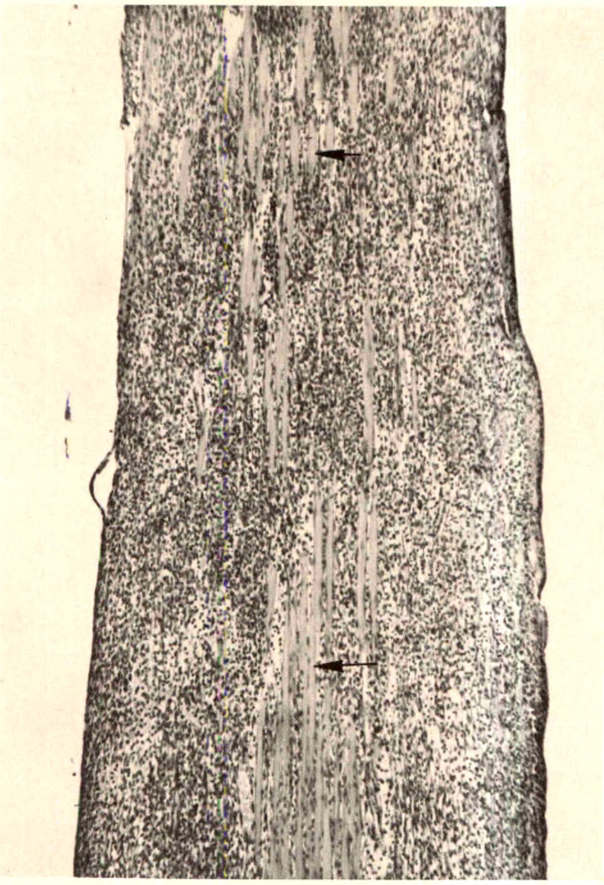


FIG 2. Longitudinal section through the EDL muscle of the rat 40 hours after a single injection of mepivacaine. Almost all of the muscle fibers have been damaged and are being broken down by macrophages. Only small numbers of intact muscle fibers (arrows) are seen in this section. H&E; 100×.

The development of myocytes in these lesions followed a pattern similar to that seen in the single injection lesions. Phagocytosis and subsequent regeneration once again appeared to move from the periphery of the lesion inward and the large repeated injection lesions contained prominent gradients of maturity between the periphery and the center of the lesion (Fig 6). Large, highly basophilic, degenerated muscle fibers, often associated with giant cells, were observed toward the center of the lesion around the 4th day after completion of the injection schedule in all three repeated injection series, but they disappeared before the 6th day. A similar pattern was observed in series C, in which such bodies were also present for several hours after the last injection (Fig 7).

The restoration of normal muscle architecture 20 days after the completion of a series of repeated injections was, in general, surprisingly good considering the massive and acute damage that their short-term counterparts were observed to have suffered. However, some evidence of possible permanent damage was observed. There were many more fibers with central nuclei in these muscles as compared with controls and singly injected long-term muscles. Scarring and regions of atrophied fibers were also observed (Fig 8). Such damage was most prevalent in series C and least prevalent in series A.

## Discussion

The results of this study demonstrate that exposure to mepivacaine can injure skeletal muscle. The etiology and clinical implications of these findings are less certain, but some inferences can be drawn.

The histologic picture of non-nucleated and fragmenting fibers surrounded by phagocytic degeneration in an edematous muscle is characteristic of ischemic necrosis. This is consistent with the finding of a characteristic lag in phagocytosis and subsequent regeneration toward the core of the lesion. These results leave little doubt that there is some interference with the vasculature in the area of the lesion. Although mepivacaine has previously been reported to possess some vasoconstrictive activity,[11, 15] it is by no means clear that its vasoconstrictive or vasodestructive activity is the only mechanism whereby mepivacaine may produce local toxic responses. Stygall et al[16] have recently reported the inhibition of myoblast fusion and the disruption of myotube structure in vitro by mepivacaine and other local anesthetics.

In the presence of an ischemic lesion, it is not possible to determine histologically whether or not there is also a primarily myotoxic effect of mepivacaine. This is in marked contrast to primarily myotoxic drugs, such as bupivacine,[4] which produce local destruction of muscle fibers without significantly compromising the blood supply. After injection of 0.5% or 0.75% bupivacaine, no focus of ischemic necrosis is present at the site of injection, and the damaged muscle fibers are all removed by phagocytosis and replaced by regenerating muscle fibers within 3 to 4 days. In the case of mepivacaine, the damage caused by ischemia is so pronounced that it obscures any possible direct damage to the muscle fibers produced by the anesthetic. Recent comparisons of the effects of intramuscular injections of seven local anesthetics in clinically recommended concentrations (A. Foster and B. M. Carlson, in preparation) have shown a similar subdivision into lesions characterized by foci of ischemic necrosis or by muscle damage alone in the absence of a vascular lesion.

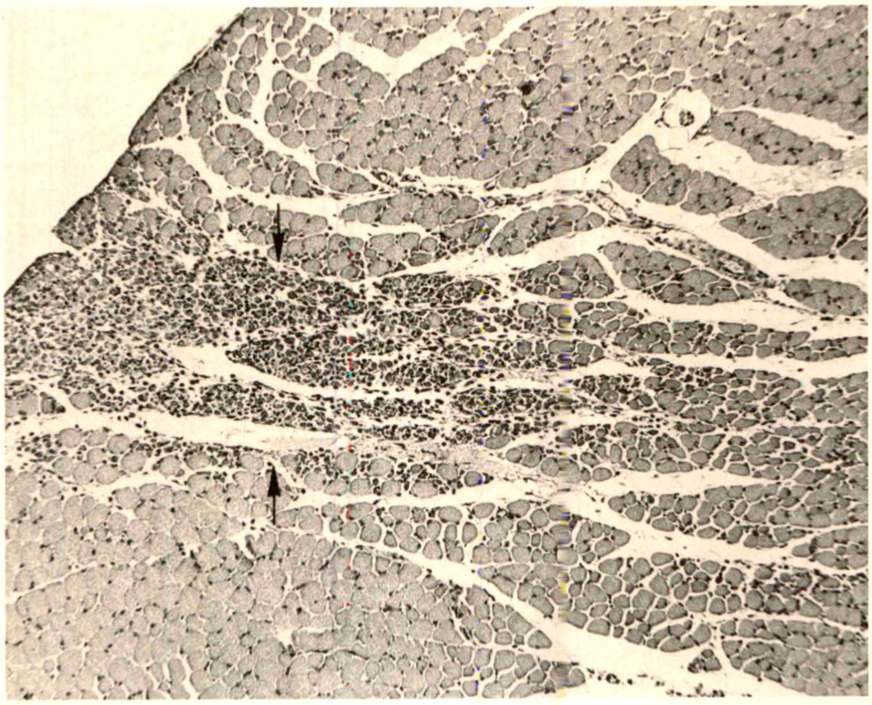


FIG 3. Cross-section through the EDL muscle 3 days after exposing the surface of the muscle to 50 $\mu$l of mepivacaine. In one area (arrows) some anesthetic apparently penetrated the muscle and caused a focus of muscle damage. This lesion is at the final stage of removal of old muscle and at the period of early myoblast formation. H&E; 100×.

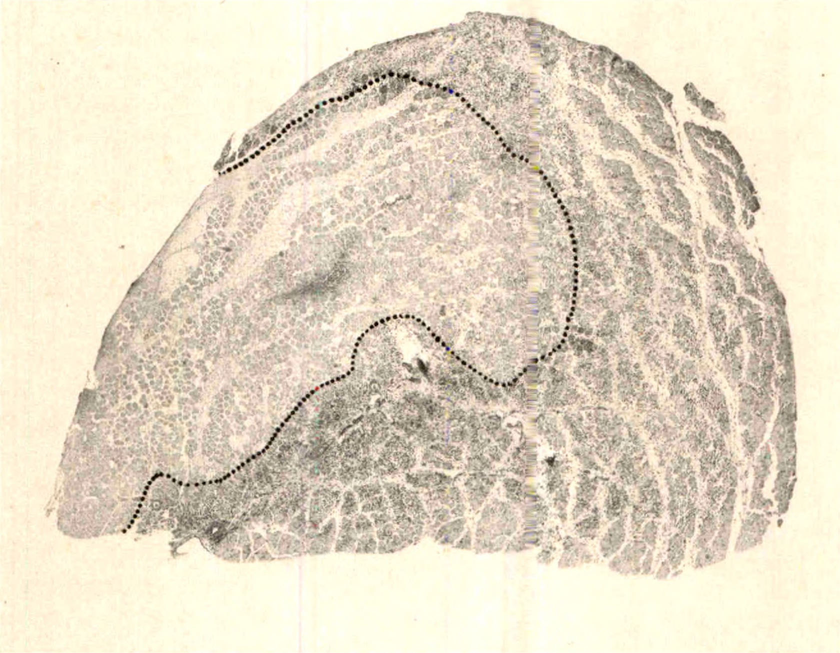


FIG 4. Cross-section through an entire tibialis anterior muscle 2 days after the muscle had been injected with mepivacaine every 2½ hours for 6 times. A large area of ischemic necrosis (dotted lines) occupies much of the muscle. The size of this lesion is typical of the others formed in this series. Just peripheral to this area is a thin zone of muscle degeneration and regeneration. H&E; 22×.

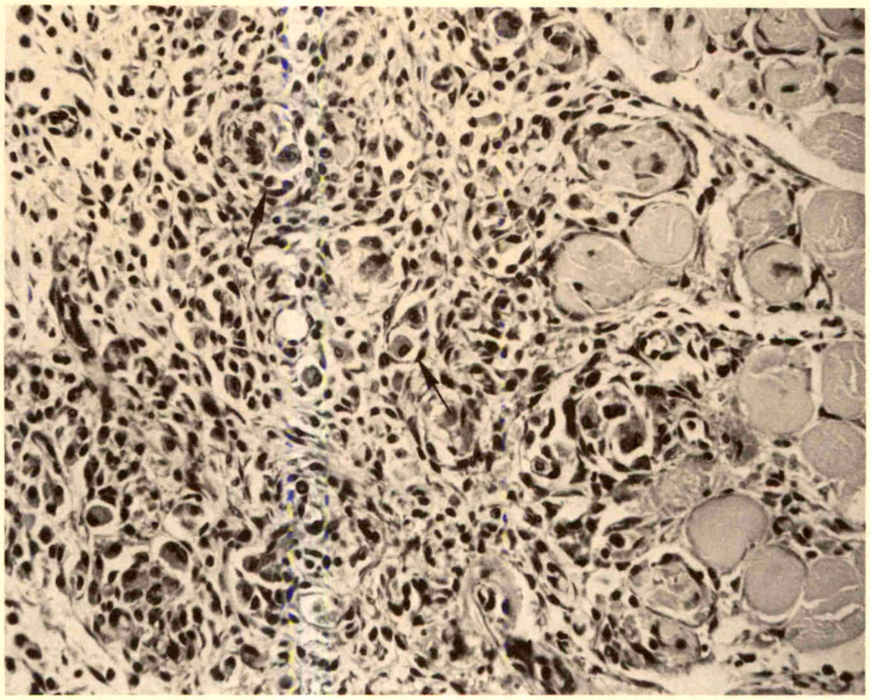


FIG 5. High power view through a lesion caused by mepivacaine injection into the tibialis anterior muscle every 4 days for 20 days. The muscle fibers at the right are necrotic. At the left, macrophages are removing damaged muscle cytoplasm and myoblastic cells are lining up beneath the persisting basal laminae (arrows). There is more cellular activity in the interstitial connective tissue than after a single injection of the anesthetic. H&E; 400×.

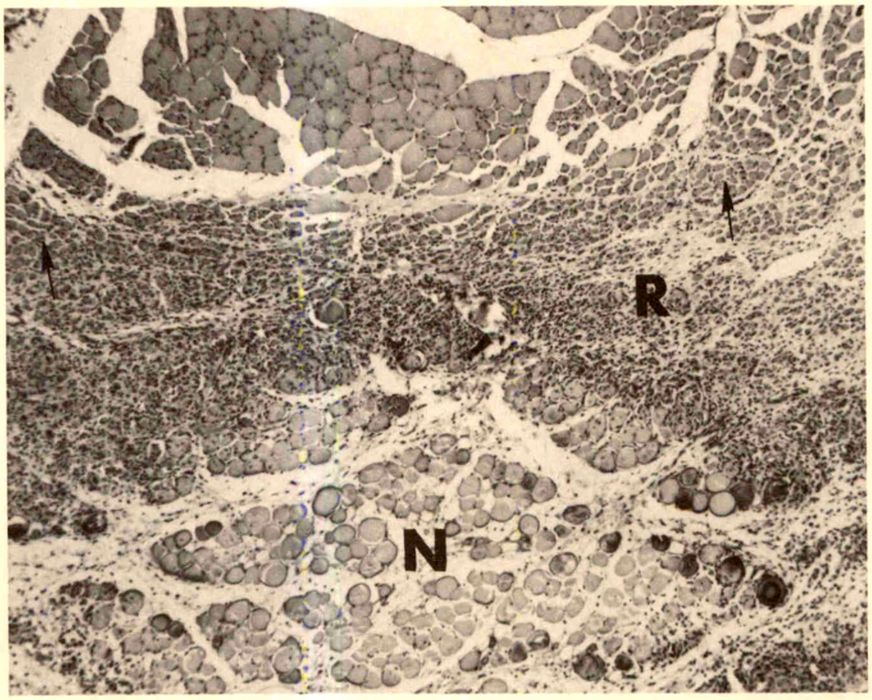


FIG 6. Cross-section through the tibialis anterior muscle 7 days after receiving six injections of mepivacaine every 4 days. A focus of necrotic muscle fibers (N) and relatively normal muscle fibers (top) are seen. Between these two areas is a region of regenerating muscle fibers (R), which are considerably more mature (arrows) near the normal muscle than near the necrotic focus. H&E; 63×.

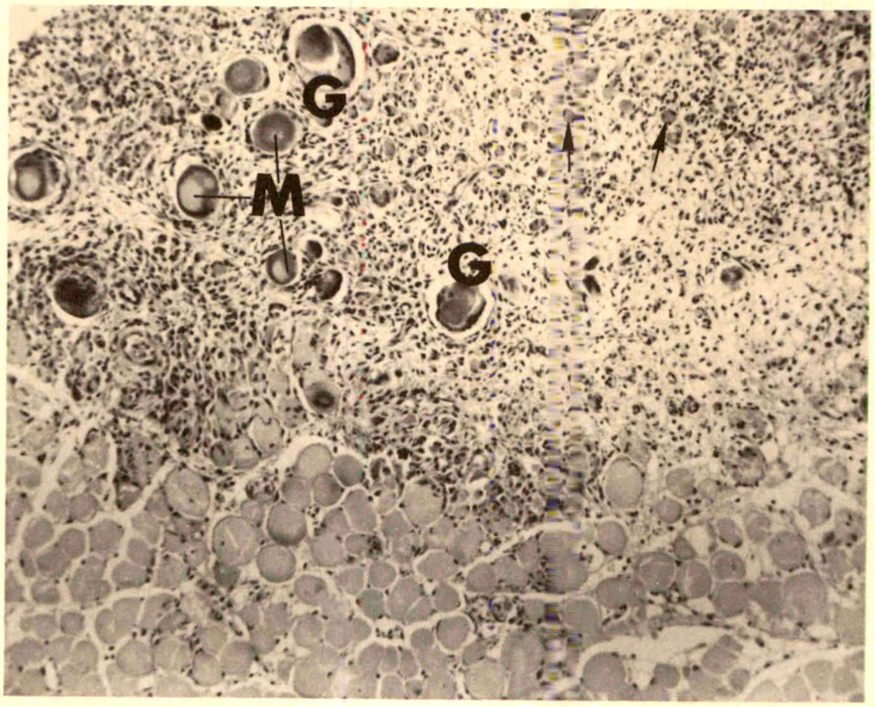


FIG 7. Persistence of abnormally degenerating basophilic muscle fibers (M) at the edge of the necrotic focus of a muscle that had received six separate injections of mepivacaine 4 days apart. The tissue was fixed on the day of the last injection. Some giant cells, possibly muscle giant cells (G), are associated with these cells. The muscle fibers at the bottom are necrotic. The region above the necrotic area is characterized by the proliferation of interstitial connective tissue and the regeneration of new muscle fibers (arrows) in the myotube stage. H&E; 100×.

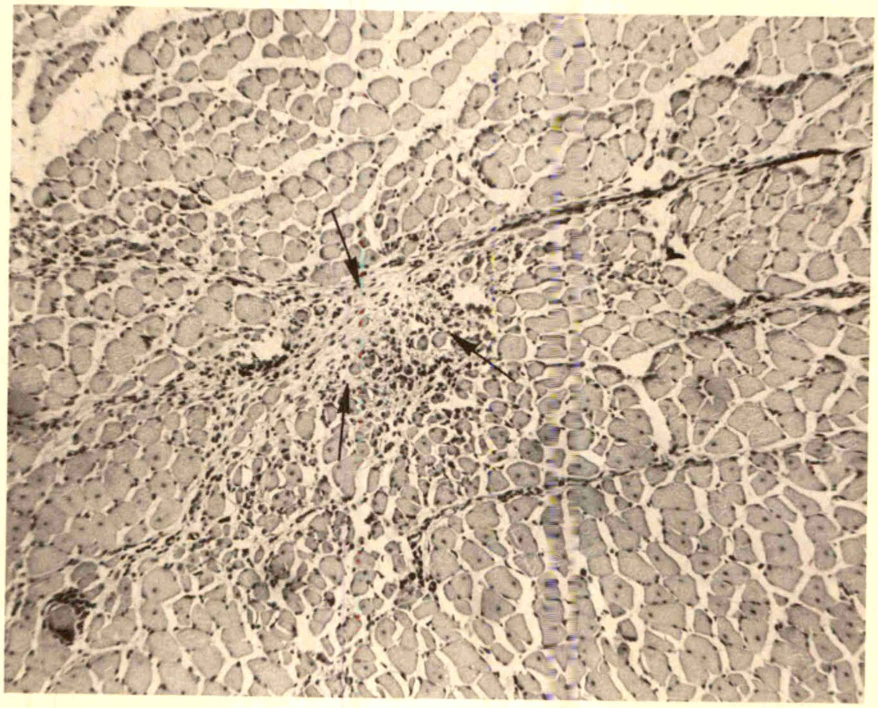


FIG 8. Cross-section through the tibialis anterior muscle 20 days after a series of six injections of mepivacaine every 2½ hours. A focus of increased connective tissue and smaller than normal regenerating muscle fibers (arrows) marks the site of a formerly severely damaged region. The central nuclei in most of the other muscle fibers show that essentially all of the muscle fibers here have broken down and subsequently regenerated. H&E; 100×.

Lesions associated with repeated injection differed from their single injection counterparts in several ways. The larger sizes of lesions were presumably due to destruction of confining fascial planes by earlier injections, thus permitting the mepivacaine injected later to diffuse outward. The greater delay in phagocytosis and regeneration toward the core was most likely associated with the larger sizes of the lesions.

The complex and chaotic histologic picture of the lesions following repeated injections can most likely be attributed ot the repeated trauma of already traumatized muscle. The large basophilic bodies are most likely pathologically altered muscle fibers, and the giant cells associated with them are characteristic of long-standing, but not acute, lesions to muscle. An important aspect of myotoxicity after repeated injections of anesthetics is the relative sensitivity of the various stages of regenerating muscle to the anesthetic. Although our model was not homogeneous enough to make any definitive statements, the histologic picture suggested that myoblasts are less sensitive than multinucleated muscle fibers. This possibility should, however, be verified on controlled in vitro systems.

This study demonstrates that mepivacaine, injected directly into or infiltrated onto the muscles of rats, causes the breakdown of muscle fibers. The damage, however, is repaired by the regeneration of new muscle fibers in the lesion. The toxic effects of a single injection are almost completely erased by regeneration of new muscle whereas repeated injections result in some long-term scarring. Laboratory studies have shown that in many respects primate muscle regenerates in a manner similar to rat muscle,[17] but our knowledge of human muscle regeneration is too incomplete to allow one to make an unqualified statement that an agent that causes muscle damage in a rat will cause similar dimage in man. Nevertheless, one should be aware of the possibility that mepivacaine might cause damage to human muscle.

Although under most circumstances mepivacaine or other local anesthetics are normally not injected directly into muscles, intramuscular injections are performed in cases of local trauma, in a number of surgical and dental procedures, in the treatment of myalgia, as well as inadvertently. The results of this study suggest that some of the short-term discomfort that patients occasionally note after injection of local anesthetics may, at least in part, be related to local muscle damage. Ultimately complete or nearly complete repair of any damaged muscle would, however be expected to ensue following a single injection. In procedures, such as multistage oral surgery, in which anesthetics are injected into the tongue, or some treatments of myalgia, which involve repeated injections of myotoxic local anesthetics, caution is indicated because of the evidence of increased long-term local scarring. Further studies on primates or clinical material are required in order to establish whether or not mepivacaine is myotoxic in man as well as in rodents.

## REFERENCES

1. Dripps RD, Eckenhoff JE, Vandam LD: Introduction to Anesthesia: The Principles of Safe Practice. Philadelphia, WB Saunders Co, 1977, p 258
2. Sokoll MD, Sonneson B, Thesleff S: Denervation changes produced in an innervated skeletal muscle by long-continued treatment with a local anesthetic. Eur J Pharmacol 4:179–184, 1968
3. Benoit PW, Belt WD: Destruction and regeneration of skeletal muscle after treatment with a local anesthetic, bupivacaine (Marcaine). J Anat 107:547–556, 1970
4. Hall-Craggs ECB, Singh-Seyen H: Histochemical changes in innervated and denervated skeletal muscle fibers following treatment with bupivacaine (Marcaine). Exp Neurol 46:345–354, 1975
5. Carlson BM: A quantitative study of muscle fiber survival and regeneration in normal, predenervated, and Marcaine-treated free muscle grafts in the rat. Exp Neurol 52:421–432, 1976
6. Brun A: Effect of procaine, Carbocaine and Xylocaine on cutaneous muscle in rabbits and mice. Acta Anaesthesiol Scand 3:59–73, 1959
7. Tait CA, Reese ND, David DA: A comparative study of hexylcaine, procaine and lidocaine with specific attention to tissue irritation. South Med J 51:358–366, 1958
8. Pizzalato P, Mannheimer W: Histopathologic Effects of Local Anesthetic Drugs and Related Substances. Springfield, IL, Charles C Thomas, 1961
9. Benoit PW, Belt WD: Some effects of local anesthetic agents on skeletal muscle. Exp Neurol 34:264–278, 1972
10. Seibel HR, Dolwick MF, Bush FM, et al: Electronmicroscopic study of the rat masseter muscle following injection of lidocaine. Acta Anat 100:354–365, 1978
11. Carlson BM, Gutmann E: Free grafting of the extensor digitorum longus muscle in the rat after Marcaine pretreatment. Exp Neurol 53:82–93, 1976
12. Wagner KR, Carlson BM, Max SR: Developmental patterns of glycolytic enzymes in regenerating skeletal muscle after autogeneous free grafting. J Neurol Sci 34:373–390, 1977
13. Carlson BM: The regeneration of a skeletal muscle—a review. Am J Anat 137:119–150, 1973
14. Reznik M: Current concepts of skeletal muscle regeneration, in The Striated Muscle. Edited by CM Pearson and FK Mostofi. Baltimore, Williams & Wilkins, 1973, pp 185–226
15. Adriani J: The Pharmacology of Anesthetic Drugs. Springfield, IL, Charles C Thomas, 1970
16. Stygall K, Mirsky R, Mowbray J: The effect of local anesthetics and barbituates on myogenesis and myotube integrity in rat skeletal muscle culture. J Cell Sci 37:231–241, 1979
17. Markley JM, Faulkner JA, Carlson BM: Regeneration following transplantation of skeletal muscles in monkeys. Plast Reconstr Surg 62:415–422, 1978

ANESTH ANALG
59:283-286, 1980

# Risk of Hyperkalemia in Recipients of Kidneys Preserved with an Intracellular Electrolyte Solution

**Carol A. Hirshman, MD,* Dolores Leon, MD,† Gerald Edelstein, MD,* Mark Brackebusch, MD,† Henry Casson, MD,‡ John Barry, MD,§ and Eugene Fuchs, MD‖**

---

HIRSHMAN, C., LEON, D., EDELSTEIN, G., BRACKEBUSCH, M., CASSON, H., BARRY, J., AND FUCHS, E.: Risk of hyperkalemia in recipients of kidneys preserved with an intracellular electrolyte solution. Anesth Analg 59:283–286, 1980.

Presumed hyperkalemic cardiac arrest has been reported following revascularization of kidney grafts preserved with an intracellular electrolyte solution (Collins' solution) containing potassium, 115 meq/L. We measured serum potassium levels immediately prior to and after revascularization in 21 recipients of cadaver kidneys preserved in Collins' solution for 10 to 45 hours and in 12 recipients of living related kidney grafts preserved with a solution containing potassium, 4 meq/L (Ringer's lactate). Following restoration of the circulation to the kidney, serum potassium levels increased a mean of 0.36 ± 0.07 meq/L ($p < 0.05$) and 0.14 ± 0.08 ($p$ value was not significant) in the recipients of Collins' and Ringer's flushed kidneys, respectively. Twenty of 21 recipients receiving Collins' flushed kidneys and four of 12 receiving Ringer's flushed kidneys required external iliac artery clamping during vascular anastomosis, rendering the leg ischemic. These 24 patients had serum potassium increases of 0.22 ± 0.05 meq/L when circulation to the leg was restored. This was significantly greater ($p < 0.05$) than that observed in the nine patients in whom the vascular supply to the leg was not interrupted (0.1 ± 0.05 meq/L).

In the 21 recipients of kidneys flushed with Collins' solution, the total increase in serum potassium was 0.45 ± 0.08 (mean ± SE) meq/L ($p < 0.02$) of which approximately 63% resulted from Collins' solution and 37% from the ischemic leg. In the 12 recipients of kidneys flushed with Ringer's lactate, the mean increase in serum potassium was statistically not significant. Potassium infusion from a kidney flushed with Collins' soluton and from the previously ischemic limb can produce an increase in potassium which may be clinically significant in patients with preexisting hyperkalemia.

**Key Words:** IONS, Potassium; KIDNEY, Transplantation.

---

CARDIAC ARRESTS have been reported following release of the vascular clamps in patients undergoing renal transplantation.[1, 2] In each case the donor kidney was flushed with Collins' solution, an electrolyte solution with a potassium concentration that approximates that of intracellular fluid[3] (Table 1). This solution is commonly used to preserve cadaver kidneys.[4] Increases in serum potassium have been shown to occur following release of the vascular clamps during renal transplantation.[2] The source of this potassium is not clear. The potassium could

---

* Assistant Professor of Anesthesiology.

† Instructor in Anesthesiology.

‡ Associate Professor of Anesthesiology.

§ Associate Professor of Surgery.

‖ Assistant Professor of Surgery.

Supported by the Department of Anesthesiology Research and Education Society.

Received from the Departments of Anesthesiology and Surgery, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201. Accepted for publication December 12, 1979.

Reprint requests to Dr. Hirshman, Department of Anesthesiology, University of Oregon Health Sciences Center.

**TABLE 1**
**Composition of Collins' Solution (meq/L)**

| | |
|---|---|
| Potassium | 115 |
| Sodium | 10 |
| Phosphate | 100 |
| Chloride | 15 |
| Bicarbonate | 10 |
| Dextrose | 138* |
| Magnesium sulfate | 60 |

* mmoles/l.

**TABLE 2**
**Patient Data**

| | Collins'-flushed kidney | Ringer's-flushed kidney |
|---|---|---|
| Total patients | 21 | 12 |
| Male/Female* | 14/7 | 9/3 |
| Diabetics* | 6 | 3 |
| Age in years | 35 ± 2.7† | 31 ± 3.7† |
| Range | 19–65 | 18–54 |
| Serum $K^-$ in meq/L (mean)‡ | 4.6 ± 0.16† | 4.6 ± 0.18† |
| Range | 3.2–5.7 | 3.7–5.4 |
| Succinylcholine* | 11 | 8 |
| Ischemic leg* | 20 | 4 |

* Number of patients.
† Mean ± SE.
‡ Immediately prior to induction.

originate from the cadaver kidney, from the leg in which the circulation has been interrupted during renal vascular anastomosis, or from both sources. We undertook this study to quantitate the magnitude of the rise in potassium occurring during renal transplantation, which is due to Collins' solution and which is secondary to the ischemic limb, by comparing potassium changes immediately prior to and following release of the vascular clamps in patients receiving Collins'-flushed kidneys and in patients receiving kidneys from living donors, flushed with a Ringer's lactate solution.

## Methods

Thirty-three adult patients undergoing surgery for renal transplantation were included in this study. Twenty-one patients received kidneys flushed with ice-cold Collins' solution. Twelve received kidneys from living donors flushed with ice-cold Ringer's lactate containing procaine, 1 g, and heparin, 1,000 units per liter. The two groups were similar with regard to age, A.S.A. physical status, and serum potassium level just prior to induction of anesthesia (Table 2). Six of the 21 patients (28%) receiving Collins'-flushed kidneys and three of the 12 receiving Ringer's-flushed kidneys (25%) were insulin-dependent diabetics.

Anesthesia was induced with thiopental. The use of depolarizing or nondepolarizing muscle relaxants to facilitate intubation was left to the discretion of the anesthesiologist. The proportion of patients receiving succinylcholine was similar in the two groups. Anesthesia was maintained with oxygen, nitrous oxide, and halothane. Following induction, a 13-cm, 14- or 16-gauge plastic catheter was inserted into the right internal jugular vein. Serum potassium levels were measured in blood obtained from a peripheral vein prior to induction and immediately thereafter. Potassium was again measured using blood from the central venous catheter immediately prior to and 15 seconds after starting to open the kidney graft to the circulation and after starting to restore circulation from and/or to the leg. The vascular clamps were released over 10 seconds. Three to 5 minutes elapsed between release of the vascular supply to the kidney and release of the vascular supply to the leg. pH, $P_{CO_2}$, $P_{O_2}$, and base excess were measured in eight patients immediately prior to and following release of the vascular clamps as well as at hourly intervals.

Twenty of 21 patients receiving Collins'-flushed kidneys and four of 12 patients receiving Ringer's-flushed kidneys had the renal artery anastomosed to the common or external iliac artery. In the remaining patients, the internal iliac artery was used. The kidneys were simply drained of their respective flush solutions by gravity prior to vascular anastomosis, and circulation was restored by slow release of the vascular clamps. The clamp release sequence for the renal artery to common iliac or external iliac artery anastomosis was as follows: proximal vein, proximal artery, distal vein, and distal artery. The clamp release sequence for the renal artery to internal iliac artery anastomosis was the following: proximal vein, internal iliac artery, and distal vein. Patients who developed metabolic acidosis during surgery received appropriate amounts of sodium bicarbonate. Patients with serum potassium values greater than 6 meq/L after induction of anesthesia were given insulin and glucose intravenously. Patients with diabetes were managed by either continuous intravenous infusion of 1 to 2 units of regular insulin per hour or by intermittent bolus injections of regular insulin intravenously. Blood glucose levels were measured at intervals of 30 to 60 minutes.

Serum potassium was measured using heparinized whole blood on a Orion model 30 sodium/potassium analyzer. Arterial blood gases and pH were measured on a Corning pH/blood gas analyzer model 165. Blood glucose was measured with an Ames eyetone reflectance colorimeter.

Serum potassium levels before and after release of the renal vascular clamps were compared using two-way analysis of variance and a Newman-Keuls test for multiple comparison.[5, 6] Potassium levels prior to and after release of the iliac vascular clamps were compared in the entire group by a paired *t*-test. Differences in potassium levels were compared in patients with ischemic and nonischemic legs by an unpaired *t*-test.[6]

## Results

In patients receiving cadaver kidneys flushed with Collins' solution, serum potassium levels increased from 4.52 ± 0.14 (mean ± SE) meq/L to 4.97 ± 0.14 following release of both vascular clamps ($p < 0.01$) (Table 3). In patients receiving kidneys flushed with Ringer's lactate solution from live donors, potassium changed from 4.34 ± 0.17 to 4.52 ± 0.14 meq/L ($p$ value was not significant) following release of the clamps. The maximum increase in potassium was 1.5 meq/L in a patient who received a cadaver kidney. Potassium levels were not significantly different in patients receiving Collins'-flushed and Ringer's-flushed kidney transplants prior to induction of anesthesia (Table 2) or prior to release of vascular clamps (Table 3).

Table 4 illustrates the change in potassium levels following release of each vascular clamp in each of the two groups. The average increase in all 33 patients was 0.12 meq/L following release of the vascular clamps to the leg. In patients in whom the arterial supply to the leg was interrupted, potassium increased 0.22 ± .05 meq/L. In contrast, potassium increased only 0.10 ± .05 meq/L in patients in whom the arterial supply to the leg was not interrupted. This difference was statistically significant ($p < 0.01$). Arterial pH decreased from a value of 7.42 ± 0.07 immediately prior to clamp release to 7.36 ± 0.08 immediately following clamp release ($p < 0.05$).

The change in potassium level was not significantly different in diabetic patients than it was in nondiabetic patients in either group. In the patients in whom the kidney was flushed with Collins' solution, serum potassium increased from 4.6 ± 0.14 to 5.0 ± 0.12 meq/L in nondiabetics and from 4.4 ± 0.38 to 4.7 ± 0.43 meq/L in diabetics following clamp release. In the patients in whom the kidney was flushed with Ringer's lactate, potassium changed from 4.4 ± 0.21 to 4.6 ± 0.17 meq/L in nondiabetics and from 4.0 ± 0.24 to 4.2 ± 0.18 meq/L in diabetics following clamp release.

**TABLE 3**

**Serum Potassium Levels prior to and Following Release of Both Vascular Clamps**

| | Before clamp release | After clamp release | *p* value |
|---|---|---|---|
| | *meq/L* | *meq/L* | |
| Collins'-flushed kidney | 4.52 ± 0.14* | 4.97 ± 0.14* | 0.02 |
| Ringer's-flushed kidney | 4.34 ± 0.17* | 4.52 ± 0.14* | NS |

* Mean ± SE.

**TABLE 4**

**Increase in Serum Potassium Levels following Release of Individual Vascular Clamps (meq/L)**

| | Collins'-flushed kidney | Ringer's-flushed kidney |
|---|---|---|
| Renal clamps | 0.36 ± 0.07* | 0.14 ± 0.08 |
| Leg clamps | 0.21 ± 0.07* | 0.13 ± 0.09 |

* There was a significant increase in potassium in the Collins'-flushed group after release of renal and leg clamps.

Following induction of anesthesia, three patients with elevated serum potassium levels (6.0 to 6.9 meq/L), with or without ECG changes, were given 15 units of regular insulin and 25 g of glucose intravenously. This decreased serum potassium to levels below 5 meq/L prior to application of the vascular clamps. Two of these patients were recipients of cadaver kidneys and did not have diabetes. The third patient was diabetic and received a kidney from a living related donor.

## Discussion

Our results indicate that the Collins'-flushed kidney was responsible for approximately 63% of the potassium rise and the ischemic leg for the remaining 37% of the potassium rise following release of the vascular clamps during renal transplantation Collins' solution is a preservative containing 115 meq/L of potassium.[3] Although most of this solution was drained from the kidney prior to completion of the vascular anastomosis, some of the solution remained in the kidney and entered the circulation as a bolus when the vascular clamps were released. Intravenous injections of 0.1 meq/kg of potassium have been shown to result in transient peak plasma potassium levels of 10 meq/L.[7] The peak plasma potassium levels observed during renal transplantation are also influenced by the rate at which the vascular clamps are removed.[2] Soulillou et al[2] were able to halve the increase in serum potassium by slow release of the clamps (release over 15 to 20 seconds). Slow release was employed in our study to decrease the peak potassium level.

Three of our patients developed elevated serum potassium levels following induction of anesthesia. Factors contributing to hyperkalemia in the patient with chronic renal failure include succinylcholine,[8, 9] metabolic acidosis,[10] hyperglycemia,[11] and aldosterone deficiency.[11] Patients with increased or rising serum potassium levels were treated in the present study with infusions of insulin and glucose prior to application of vascular clamps. This resulted in potassium levels in the normal range in all patients prior to release of the vascular clamps. No patient developed cardiac arrhythmias or T-wave changes on the electrocardiogram following release of the vascular clamps.

There was a small but significant increase in potassium following release of the vascular clamps to the limb in patients receiving kidneys flushed with Collins' solution but not in patients receiving kidneys from living donors (Ringer's lactate-flushed). The reason for this difference is most likely related to the type of vascular anastomosis performed. Anastomosis of the renal artery to the internal iliac artery does not produce ischemia to the limb whereas anastomosis of the renal artery to the common or external iliac artery results in ischemia to the leg while the anastomosis is being performed. In most of the patients who received kidneys from living related donors (Ringer's-flushed), the internal iliac artery was used, whereas many patients receiving cadaver kidneys (Collins'-flushed) had had previous renal transplants, internal iliac arteriosclerosis, or multiple renal arteries on an aortic patch, making it necessary to anastomose the renal artery to either the common or external iliac artery, producing ischemia in that limb while the vascular anastomoses were being performed. A small but significant acidosis was noted following vascular clamp release reflecting restoration of circulation to the leg. This acidosis may be responsible for much of the increase in potassium level seen following release of the vascular clamps to the leg.

Because patients with chronic renal failure who have diabetes mellitus may be more prone than nondiabetic patients to develop hyperkalemia during renal transplant surgery,[11] we evaluated this small subgroup separately. Diabetic patients received insulin appropriately throughout surgery. Diabetics who received a Collins'-flushed kidney had elevations of serum potassium in the same range as did nondiabetics following clamp release.

Although the increase in serum potassium levels may not be clinically important in all patients, it may well be detrimental in patients with renal failure who come to surgery with or who subsequently develop elevation of serum potassium levels. Our study demonstrates increases in potassium levels as great as 1.5 meq/L. This elevation could result in levels in the range where significant arrhythmias or cardiac arrest might occur in patients in whom serum potassium was already elevated.

We recommend frequent monitoring of serum potassium in patients with chronic renal failure who are receiving cadaver kidneys flushed with potassium-rich (Collins') solution. Moreover, efforts should be made to minimize the rise of potassium at the time of release of vascular clamps. These efforts include prior drainage of the kidney, slow release of clamps restoring circulation to both the kidney and the ischemic leg, and treatment of preexisting hyperkalemia. Potassium from a Collins'-flushed kidney and from a previously ischemic limb can produce a small increase in serum potassium, which may be clinically significant in patients with preexisting hyperkalemia.

## ACKNOWLEDGMENT

The authors thank Frances Cetinich for her help in typing and editing our manuscript.

## REFERENCES

1. Hirshman CA, Edelstein G: Intraoperative hyperkalemia and cardiac arrests during renal transplantation in an insulin dependent diabetic. Anesthesiology 51:161–162, 1979
2. Soulillou JP, Fillaudeau F, Keribin JB, et al: Acute hyperkalemia risks in recipients of kidney graft cooled with Collins' solution. Nephron 19:301–304, 1977
3. Hardie I, Balderson G, Hamlyn L, et al: Extended ice storage of canine kidneys using hyperosmolar Collins' solution. Transplantation 23:282–283, 1977
4. Hartley LCJ, Collins GM, Clunie, GJA: Kidney preservation for transportation. N Engl J Med 285:1049–1052, 1971
5. Scheffé H: Analysis of Variance. First Edition. New York, John Wiley, 1959
6. Steele RC, Torrie J: Principles and Procedures of Statistics. Second Edition. New York, McGraw-Hill, 1960, pp 110–112
7. Tanaka K, Pettinger WA: Pharmacokinetics of bolus potassium injections for cardiac arrhythmias. Anesthesiology 38:587–589, 1973
8. Miller RD, Way LW, Hamilton WK, et al: Succinylcholine-induced hyperkalemia in patients with renal failure. Anesthesiology 36:138–141, 1972
9. Koide M, Waud BE: Serum potassium concentrations after succinylcholine in patients with renal failure. Anesthesiology 36:142–145, 1972
10. Strunin L: Some aspects of anaesthesia for renal homotransplantation. Br J Anaesth 38:812–822, 1966
11. Cox M, Sterns RH, Singer I: The defense against hyperkalemia: the role of insulin and aldosterone. N Engl J Med 299:525–532, 1978

ANESTH ANALG
59:287-290, 1980

# Gastric Fluid Volume and pH after Fentanyl, Enflurane, or Halothane-Nitrous Oxide Anesthesia with or without Atropine or Glycopyrrolate

**Robert K. Stoelting, MD***

---

STOELTING, R. K.: Gastric fluid volume and pH after fentanyl, enflurane, or halothane-nitrous oxide anesthesia with or without atropine or glycopyrrolate. Anesth Analg 59:287-290, 1980

Gastric fluid volume and pH were determined immediately following the induction of anesthesia and again after 2 hours of anesthesia consisting of 60% nitrous oxide plus either fentanyl, enflurane, or halothane. Adult patients undergoing elective, but not upper abdominal, operations were subjects for this study. Preanesthetic medication included intramuscular morphine with or without either atropine (0.4 mg) or glycopyrrolate (0.2 mg). Gastric fluid volume after 2 hours of anesthesia was significantly less ($p < 0.05$) than immediately after induction of anesthesia. Gastric volume was similar for all anesthetics and was not influenced by the inclusion of anticholinergic drugs in the preanesthetic medication. Compared with control gastric pH (only patients with an initial pH less than 3.5 were studied) there was no change in pH after 2 hours of fentanyl anesthesia with or without either atropine or glycopyrrolate. Likewise, pH did not change during halothane anesthesia without anticholinergic drugs. Enflurane anesthesia with or without anticholinergic drugs and halothane combined with atropine or glycopyrrolate were associated with significant increases ($p < 0.05$) in gastric pH. Glycopyrrolate was associated with greater increases in pH than was atropine ($p < 0.05$). These data suggest that gastric fluid production is minimal during anesthesia irrespective of anesthetic drugs or preanesthetic medication. Halothane or enflurane, but not fentanyl, when combined with glycopyrrolate preanesthetic medication was associated with the greatest increase in gastric pH. However, the increased pH was not seen in all patients and often the increase was not sufficiently great to protect against pneumonitis should aspiration have occurred.

**Key Words:** GASTROINTESTINAL TRACT, stomach; ANESTHETICS, Volatile: halothane; ANESTHETICS, Volatile: enflurane; ANALGESICS, fentanyl.

---

INHALATION anesthetics produce a dose-dependent decrease in hydrogen ion secretion from isolated gastric mucosa.[1] In man, gastric fluid pH is increased during halothane, unchanged during cyclopropane, and variably altered during fluroxene anesthesia.[2] Effects of fentanyl or enflurane on gastric fluid pH have not been determined. This report describes gastric fluid volume and pH before and after 2 hours of anesthesia with nitrous oxide plus fentanyl, enflurane, or halothane. In addition, the influence of anticholinergic preanesthetic medication on gastric fluid volume and pH after 2 hours of anesthesia was evaluated.

## Methods

Adult patients (A.S.A. class I-II) undergoing elective 8 a.m. operations (excluding upper abdominal

---

* Professor and Chairman.

Received from the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana 46223. Accepted for publication December 15, 1979.

procedures) were studied. The study was approved by the Indiana University School of Medicine Clinical Research Committee. No patient had a disease process or was taking drugs known to influence gastric secretion. Preanesthetic medication consisted of intramuscular morphine (8 to 12 mg) with or without an anticholinergic (atropine, 0.4 mg, or glycopyrrolate, 0.2 mg) 60 to 90 minutes before induction of anesthesia. Anesthetic induction was with gallamine, 0.3 mg, followed 3 minutes later with thiamylal, 4 to 5 mg/kg, plus succinylcholine, 2 mg/kg, to facilitate tracheal intubation. Pancuronium was used for relaxation as indicated. Immediately following tracheal intubation a 18-French gastric tube (sump-type) was placed in the stomach. Gastric fluid was aspirated for control measurements of gastric volume and pH (Corning pH meter and Beckman electrode). Only patients with a gastric fluid pH of 3.5 or less were included in the study. Patients with a gastric pH above 3.5 were arbitrarily excluded based on the speculation that gastric hydrogen ion secretion was already minimal and further reduction by anesthetic drugs would be masked in these patients. Patients were divided in groups as shown in Table 1.

Anesthesia was maintained with inspired concentrations of 60% nitrous oxide plus 0.3% to 1% halothane or 0.5% to 2% enflurane. Fentanyl was administered as a 2 μg/kg loading dose followed by 50 μg every 15 minutes. After 2 hours of anesthesia gastric fluid was again aspirated and volume and pH measured.

Mean gastric fluid pH was calculated using the individual pH values.[3] Data were analyzed by two-way analysis of variance using a 3 x 3 table design adjusted for unequal cell frequencies. Individual comparison *t*-tests were carried out for each preanesthetic medication and anesthetic group. $P < 0.05$ was considered statistically significant.

**TABLE 1**
**Patient Groups**

| Preanesthetic medication (in addition to morphine) | Anesthetic (in addition to nitrous oxide) | No. of patients | Age* | Weight* |
|---|---|---|---|---|
| | | | *yr* | *kg* |
| None | Fentanyl | 10 | 44 ± 4 | 77 ± 4 |
| | Enflurane | 14 | 39 ± 4 | 67 ± 5 |
| | Halothane | 10 | 32 ± 4 | 71 ± 5 |
| Atropine | Fentanyl | 10 | 30 ± 4 | 69 ± 3 |
| | Enflurane | 10 | 47 ± 7 | 76 ± 4 |
| | Halothane | 9 | 44 ± 5 | 69 ± 4 |
| Glycopyrrolate | Fentanyl | 8 | 43 ± 6 | 73 ± 4 |
| | Enflurane | 10 | 33 ± 5 | 67 ± 5 |
| | Halothane | 10 | 40 ± 5 | 74 ± 5 |

* Values are means ± SE.

**TABLE 2**
**Gastric Fluid Volume***

| | Control† | After 2 hours of anesthesia |
|---|---|---|
| | *ml* | |
| Fentanyl | 29 ± 6 | 7 ± 2‡ |
| Enflurane | 23 ± 9 | 7 ± 1‡ |
| Halothane | 33 ± 13 | 7 ± 3‡ |
| Fentanyl-atropine | 16 ± 10 | 4 ± 3 |
| Enflurane-atropine | 19 ± 6 | 9 ± 3‡ |
| Halothane-atropine | 20 ± 8 | 4 ± 1‡ |
| Fentanyl-glycopyrrolate | 27 ± 9 | 9 ± 3‡ |
| Enflurane-glycopyrrolate | 19 ± 4 | 5 ± 2‡ |
| Halothane-glycopyrrolate | 22 ± 3 | 8 ± 2‡ |

* Values are means ± SE.
† Immediately after induction of anesthesia.
‡ $p < 0.05$ vs control.

## Results

Control gastric fluid volume measurements were similar in all groups (Table 2). Fluid volume after 2 hours of anesthesia was significantly less ($p < 0.05$) than it was immediately following induction of anesthesia (Table 2). This volume was similar for all anesthetics and was not influenced by use of atropine or glycopyrrolate in the preanesthetic medication.

Gastric pH levels before and after 2 hours of anesthesia with or without anticholinergic drugs included in the preanesthetic medication are shown in the Figure. Fentanyl anesthesia with or without atropine or glycopyrrolate and halothane anesthesia without anticholinergic drugs were not associated with significant changes in gastric pH. Enflurane anesthesia with or without anticholinergic drugs and halothane combined with atropine or glycopyrrolate were associated with increases in pH ($p < 0.05$). Glycopyrrolate plus halothane or enflurane was associated with a greater increase in pH than were the same anesthetics combined with atropine ($p < 0.05$). No anesthetic or anticholinergic combination was reliably associated with elevation of gastric fluid pH in the majority of patients (Figure).

## Discussion

The development of pneumonitis after inhalation of gastric fluid depends on the pH and volume of the

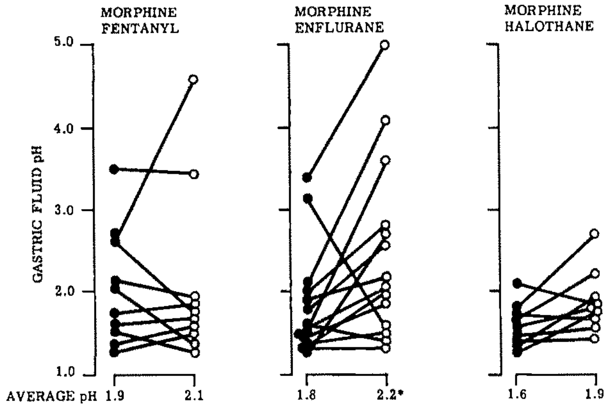


FIGURE. Individual and average gastric fluid pH values present immediately after anesthetic induction (control, solid circles) and after 2 hours of anesthesia with 60% nitrous oxide plus fentanyl, enflurane, or halothane (open circles). Preanesthetic medication consisted of intramuscular morphine with or without atropine or glycopyrrolate. * $p < 0.05$ compared with control pH.

aspirated fluid. Therefore, any ability of anesthetic drugs alone or in combination with anticholinergics to decrease gastric fluid secretion or reduce hydrogen ion production could protect against pneumonitis should aspiration occur intraoperatively or at the conclusion of the anesthetic.

Gastric pH after 2 hours of anesthesia was related to the specific anesthetic drugs administered and the inclusion of atropine or glycopyrrolate in the preanesthetic medication. Fentanyl with or without atropine or glycopyrrolate was not associated with significant changes in gastric fluid pH. Likewise, gastric pH was not changed from control values in patients receiving halothane for 2 hours without inclusion of anticholinergics in the preanesthetic medication. Our data with halothane differ from an earlier report[2] describing an increase in gastric fluid pH from 1.8 before to 7.5 after 90 minutes of halothane administration. This increase in pH was attributed to depression of the parasympathetic nervous system produced by halothane. Our data suggest that parasympathetic and/or sympathetic nervous system activity is not sufficiently altered by fentanyl or halothane to result in reduced gastric hydrogen ion secretion. In contrast enflurane was associated with a statistically significant but clinically insignificant increase in gastric pH. This suggests that enflurane is the only one of the anesthetic drugs studied capable of detectably altering gastric hydrogen ion secretion. The mechanism by which enflurane increased gastric pH cannot be determined from this study.

Gastric fluid volume after 2 hours of anesthesia was minimal regardless of the anesthetic administered or the inclusion of anticholinergics. The mechanism of decreased gastric fluid secretion is not clear but may represent a generalized depressant effect common to the anesthetics. Atropine or glycopyrrolate did not contribute to the low gastric fluid volumes; volumes were the same with or without anticholinergic drugs. Although volumes were consistently decreased compared with control measurements it is never possible to ensure that all gastric fluid has been aspirated. As such our gastric fluid volume measurements are conservative estimates of the total volume present.

Anticholinergic drugs would seem more likely than anesthetics to decrease parasympathetic activity and reduce gastric fluid volume and hydrogen ion secretion. However, in a previous study preanesthetic medication including atropine, 0.4 mg, or glycopyrrolate, 0.2 mg, did not influence gastric fluid volume or pH at the time of anesthetic induction.[4] The present data confirm the absence of a detectable effect of these anticholinergic doses on gastric fluid volume after 2 hours of anesthesia. Likewise, anticholinergics were not effective in raising gastric fluid pH after fentanyl. In contrast, use of atropine or glycopyrrolate prior to halothane anesthesia significantly increased gastric fluid pH above control measurements. The magnitude of this increase in pH was greater after glycopyrrolate than after atropine ($p < 0.05$). This is consistent with the longer duration and greater inhibition of hydrogen ion secretion that occurs with glycopyrrolate.[5] It is of interest that the previous report describing an increased gastric fluid pH with halothane[2] was observed in patients also receiving atropine or scopolamine as preanesthetic medication. The effect of anticholinergics prior to enflurane is less clear as this anesthetic alone significantly increased gastric fluid pH by an amount similar to that seen when atropine was utilized in the preanesthetic medication.

In summary, halothane or enflurane but not fentanyl when combined with glycopyrrolate preanesthetic medication was associated with the greatest increase in gastric pH after 2 hours of anesthesia. It must be emphasized that the increase was not seen in all patients and often the increase was not sufficiently great to protect reliably against pneumonitis should aspiration have occurred. A consistent observation, regardless of the anesthetic technique, was the small gastric fluid volume present after 2 hours of anesthesia. However, to ensure the presence of a minimal volume the stomach must be routinely aspirated prior to the conclusion of anesthesia.

REFERENCES

1. MacKrell T, Schwartz M: Effects of volatile anesthetics on nonexcitable tissue. Anesthesiology 30:345, 1969
2. Christensen V, Skovsted P: Effects of general anaesthetics on the pH of gastric contents in man during surgery: a survey of halothane, fluroxene and cyclopropane anaesthesia. Acta Anaesthesiol Scand 19:49–54, 1975
3. Feinstein AR: On central tendency and the meaning of mean for pH values. Anesth Analg 58:1–3, 1979
4. Stoelting RK: Responses to atropine, glycopyrrolate and Riopan of gastric fluid pH and volume in adult patients. Anesthesiology 48:367–369, 1978
5. Wyant GM, Kao K: Glycopyrrolate methobromide. I. Effect on salivary secretion. Can Anaesth Soc J 21:230–241, 1974

---

## Complications of Pulmonary Artery Catheterization

In order to evaluate the incidence and significance of complications resulting from the use of flow-directed, balloon-tipped catheters to monitor critically ill patients, a prospective study of 116 pulmonary artery catheterizations was performed. Indications for catheterization included shock, pulmonary edema, or hemodynamic instability following surgery. Arrhythmias, including premature atrial or ventricular depolarizations, ventricular tachycardia, and transient right-bundle branch block occurred during 90 of the 116 insertion procedures, but were not associated with morbidity or mortality. In two patients (1.7%) staphylococcal bacteremia probably originated from the catheter. In addition, the pulmonary artery catheter led to two cases (1.7%) of subclavian vein thrombosis. Postmortem examinations revealed perforations of the pulmonic valve in one case. The authors conclude that although significant complications may result from pulmonary arterial catheterization and monitoring of critically ill patients, the incidence is low and the ratio of benefits to complications is favorable. *(Elliott CG, Zimmerman GA, Clemmer TP: Complications of pulmonary artery catheterization in the care of critically ill patients. Chest 76:647–652, 1979)*

# CLINICAL reports

# The Tracheal Tube Cuff Pressure Stabilizer and Its Clinical Evaluation

Jong-Min Kim, MD*

The trachea is not round on cross-section but rather more imperfectly circular with a flattened posterior segment. To achieve a tracheal seal with a low-volume, high-pressure cuff, the tracheal wall must be deformed to the circular rigid cuff. This results in uneven distribution of pressure on the tracheal wall and requires high tracheal wall pressure to assure a gas-tight seal.[1,2] The high tracheal wall pressure with such cuffs has been considered a major factor contributing to tracheal complications following long-term intubation with a high-pressure cuffed tube. This has led to the use of large-volume, low-pressure cuffed tracheal tubes for patients in intensive care units and during operation.

The large-volume, low-pressure cuff provides a tracheal seal with low intracuff pressures by deforming its own shape to conform to the tracheal lumen. The cuff then exerts more evenly distributed pressure around the tracheal wall.[3] However, when large-volume, low-pressure endotracheal tube cuffs are used during anesthesia, intracuff pressure can be increased to levels equal to arterial blood pressure due to volume expansion of cuff air.[4] The volume expansion is mainly caused by diffusion of anesthetic gases into the air-containing cuff and, to a lesser extent, caused by warming of air in the cuff to body temperature.

Several suggestions have been proposed to maintain low intracuff pressures intraoperatively, including intermittent deflation of cuff, inflation of the cuff with anesthetic gas mixtures, etc. Commercially available devices designed to prevent increase in cuff pressures can be divided into two types: (1) tracheal tubes that have cuff pressure control devices (usually the whole unit is disposable) and (2) pressure relief valves that connect to the inflating port of the cuff catheter (usually not disposable). The first includes the Kamen-Wilkinson tracheal tube with "Fome-Cuff" (Bivona), the Dupaco "Liqui-Seal" tracheal tube, and the Lanz tracheal tube "controlled pressure" cuff with pressure-regulating balloon and volume-regulating check valve. The second group includes the cuff pressure regulator (Boehringer Laboratory) and the pressure relief valve reported by Stanley and associates.[5] These devices are either expensive or difficult to assemble. The present report introduces a newly designed "Tracheal Tube Cuff Pressure Stabilizer" (TTCPS) which belongs to the latter type of device.

## Design and Operation

The basic idea for the design was adapted from the principle of the underwater seal used for positive end-expiratory pressure ventilation.

The TTCPS is easily built as shown in Fig 1. Either transparent Plexiglas or plastic tubing is used as a water container, measuring approximately 1.5 cm i.d. and 50 cm in height (Fig 1, 1). The unit also contains a disposable central venous pressure manometer (Fig 1, 2), a vent needle (Fig 1, 3), a three-way stopcock (Fig 1, 4), a C.F.S. Intraflo (continuous flush system; Sorenson Research Co., Salt Lake City, UT) (Fig 1, 5), and an extension tube (Pressure Transmission Set (84-inch tubing) Cutter Laboratories, Inc., Berkeley, CA) (Fig 1, 6).

After these parts are assembled, the unit can be attached to a supporting upright of the anesthesia

---

* Associate Professor.

Received from the Department of Anesthesiology, University of Kansas College of Health Sciences and Hospital, 39th and Rainbow Boulevard, Kansas City, Kansas 66103. Accepted for publication October 19, 1979.

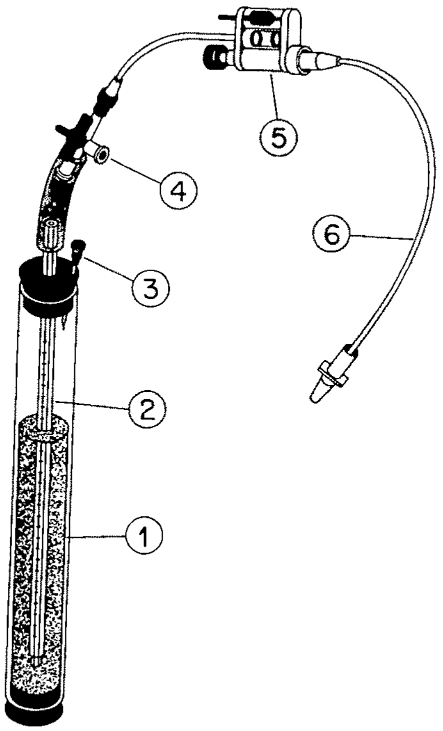


FIG 1. "Tracheal Tube Cuff Pressure Stabilizer" (TTCPS) is easily built with materials readily available in the operating room. The materials consist of a water container (1), a central venous pressure manometer (2), a vent needle (3), a three-way stopcock (4), a C.F.S. Intraflo (5), and an extension tube (6). See text for operation instructions.

machine. To prevent microbial contamination, the water container (1) is filled with benzalkonium chloride (1:750) to the proper height through the three-way stopcock (4). If water is used to fill the container, the water turns turbid after prolonged use due to microbial infestation. The height of the fluid level shown on the graduation marks of the central venous pressure manometer (2) will be the intended intracuff pressure to be maintained (cm $H_2O$).

Following tracheal intubation, the cuff is inflated with more than an adequate amount of air. The inflating port of the cuff catheter is securely connected to the male adaptor of the extension tube (6). By pulling the rubber band of the C.F.S. Intraflo (4) the excess amount of cuff air bubbles out until intracuff pressure is rapidly adjusted to the predetermined pressure. On releasing the rubber band, a subsequent rise in intracuff pressure due to diffusion of anesthetic gases is controlled to the predetermined pressure by slow mode of control (Fig 2B).

The TTCPS should be tested for any possible leaks before clinical application. The test is conducted on the overinflated cuff outside the trachea. Using the same technique as described previously, the intracuff pressure is adjusted to a predetermined value and held for 1 to 2 hours. In a tightly connected unit free of leaks, the water level on the central venous pressure manometer should not increase beyond the tip during the waiting period. An increasing water level indicates a leak in the system which should be corrected.

The C.F.S. Intraflo is originally designed to provide a slow continuous flow of the flush solution through intravascular catheter to prevent intraluminal clot formation. It is also equipped with a valve that allows a fast flush by pulling the rubber band. According to the package insert, when the flush solution is compressed to 300 mm Hg, the flow rate of the solution passing through the C.F.S. Intraflo should be 0.033 to 0.066 ml/min. If air is compressed at the same pressure, the theoretically estimated flow rate of the air will be 55 times faster than the flow rate of water because viscosity of air is 55 times less than viscosity of water. The flow rate also depends on the pressure gradient across the C.F.S. Intraflo (Hagen-Poiseuille law).

When a trachael tube is intubated into a rigid artificial trachea and the cuff is inflated with air to 100 mm Hg, the intracuff pressure decreases to 60 mm Hg in 1.5 minutes, and to 21 mm Hg in 16 minutes following the application of TTCPS. Due to the fact that the higher the intracuff pressure the faster the adjustment of the intracuff pressure, the procedure adjusting intracuff pressure rapidly by opening the fast flush valve can be omitted in clinical application of the TTCPS. The C.F.S. Intraflo retards sudden loss of intracuff air if the cuff pressure temporarily exceeds the predetermined value, such as during the inspiratory phase of intermittent positive pressure ventilation (IPPV) and during coughing.

The TTCPS can only be used with low-pressure cuffed tracheal tubes that have the ability to seal the trachea at intracuff pressures less than 40 cm $H_2O$ (30 mm Hg). If the tracheal tube is left in the patient for postoperative ventilatory or airway support, the air in the cuff should be replaced with fresh air and the intracuff pressure should be readjusted using the same technique as described above. Otherwise the tracheal seal may be broken as anesthetic gases in the cuff diffuse out postoperatively. The TTCPS can be used from patient to patient without cleaning.

## Clinical Evaluation

The TTCPS was evaluated for its effectiveness and safety in 100 endotracheally intubated patients who

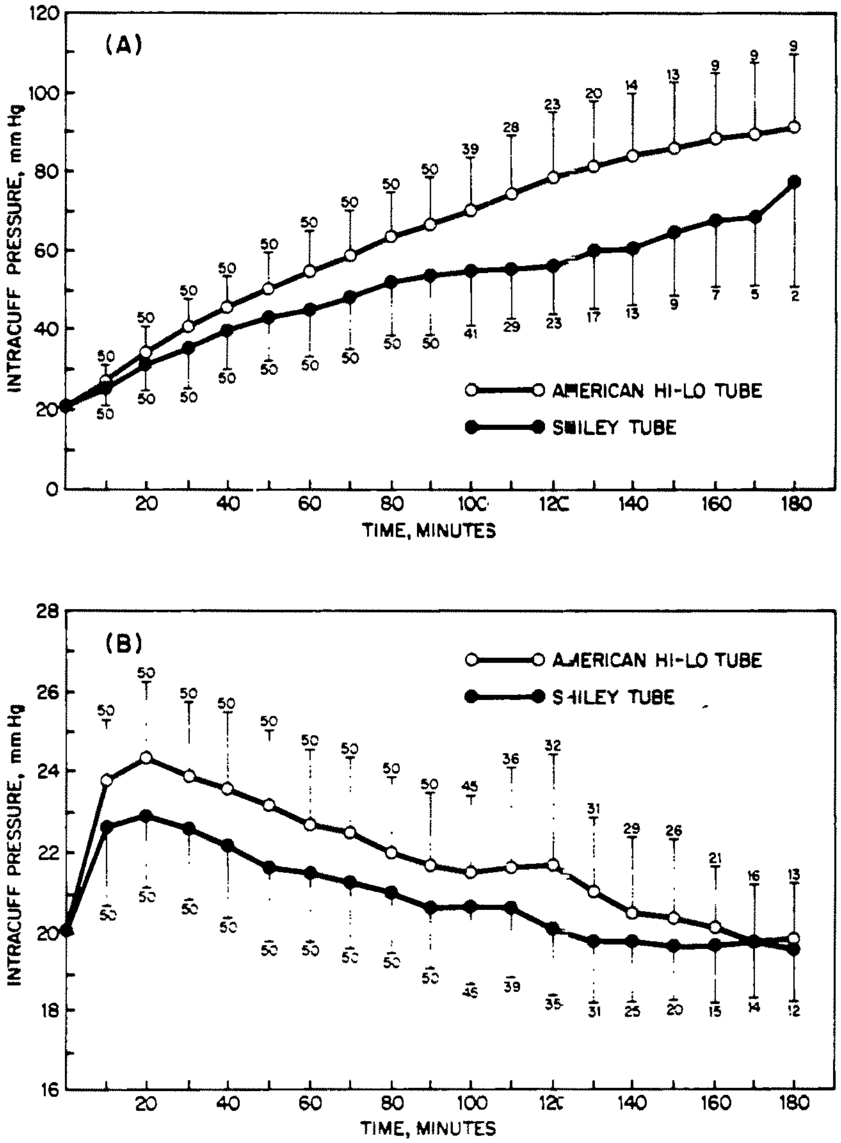


FIG 2. Intraoperative changes in intracuff pressure of the American Hi-Lo cuff (open circle) and Shiley Low Pressure cuff (solid circle) when the intracuff pressure was not controlled (A) and when it was controlled (B) by TTCPS. Intracuff pressure started at 20 mm Hg in all tubes. Vertical bars indicate standard deviation of mean. Number of tubes studied is shown at the end of each vertical bar.

underwent a variety of operative procedures performed under general anesthesia using more than 50% nitrous oxide. Fifty each of American Hi-Lo Tracheal Tubes and Shiley Low Pressure Cuffed Endotracheal Tubes were used. According to the package insert of the American Hi-Lo Tracheal Tube, an adequate tracheal seal can be obtained with an intracuff pressure under 19 mm Hg in most circumstances. Based on this recommended intracuff pressure, the predetermined intracuff pressure was chosen to be 20 mm Hg. The water container in the unit was filled to 27 cm. For continuous intracuff pressure measurement, a pressure transducer was inserted between the C.F.S. Intraflo and the extension tube by adding another three-way stopcock. The intracuff pressure was displayed as digital numerals (mm Hg) on a Datascope Monitor.

Following induction of anesthesia, the trachea was intubated with the proper sized American Hi-Lo or Shiley tracheal tube, and the cuff was inflated with air. As soon as the tracheal tube was secured in place and intraesophageal instrumentations completed (e.g. insertion of esophageal stethoscope, nasogastric tube, temperature probe, etc), the cuff air was replaced with fresh air. The extension tube of the unit was connected securely to the inflating port of the cuff catheter, and the rubber band of the C.F.S. Intraflo was pulled until the bubbling of excess cuff air ceased. The resulting intracuff pressure, which was adjusted rapidly, was recorded on the anesthesia record sheet. Any subsequent change in the intracuff pressure, which was adjusted by the slow mode, was recorded every 10 minutes until nitrous oxide was discontinued.

As a control, an additional 50 each of American Hi-Lo Tracheal Tubes and Shiley Low Pressure Cuffed Endotracheal Tubes were studied. After initial rapid adjustment, the intracuff pressure was allowed to increase by bypassing the TTCPS. Subsequent changes in intracuff pressures were recorded every 10 minutes as described above. Data obtained in surgical procedures that lasted less than 90 minutes were discarded. The anesthetic technique and size of the tracheal tube were not controlled.

## Results

On bypassing the TTCPS after rapid adjustment, the intracuff pressure increased steadily with time as anesthetic gases diffused into the cuff. The initial intracuff pressure of the American Hi-Lo cuff, 20 mm Hg, doubled after 30 minutes, tripled after 70 minutes, and quadrupled after 120 minutes. Compared to the American Hi-Lo cuff, the rate of rise in intracuff pressures of the Shiley Low Pressure cuff had a slower rate of increase in pressure and lower peak pressure (Fig 2A). In three of 23 American Hi-Lo tubes and none of 23 Shiley tubes, the intracuff pressure exceeded 100 mm Hg after 120 minutes.

With application of the TTCPS, overinflated cuffs rapidly and reliably adjusted to the preset intracuff pressure, 20 mm Hg, and this pressure was maintained within a narrow range by the slow mode of control. Following the peak intracuff pressure of 24 ± 2 mm Hg (mean ± 1 SD) in the American Hi-Lo cuff and 23 ± 2 mm Hg in the Shiley Low Pressure cuff, both reached in 20 minutes, the pressure declined gradually toward 20 mm Hg during the next 120-minute period until stabilized at this pressure (Fig 2B). The 20 mm Hg intracuff pressure provided an adequate tracheal seal for IPPV without apparent leak around the cuff except in two Shiley tubes. In one American Hi-Lo tube, the inflating port of the cuff catheter cracked intraoperatively and intracuff pressure was suddenly lost. These three tubes were excluded from the data. None of the patients developed evidence of aspiration symptoms postoperatively.

## Discussion

Large-volume, low-pressure cuffed tracheal tubes can seal the trachea at low intracuff pressures, but these low intracuff pressures cannot be maintained if proper care is not exercised during the anesthesia. Undesirably high intracuff pressures can result from enthusiastic blind inflation of the cuff or by diffusion of anesthetic gases, mainly nitrous oxide, into the air-containing cuff. When the compliance of most large-volume, low-pressure cuffs is measured outside the trachea, high values, as claimed by the manufacturers, are found. However, the compliance is no longer high in the intubated cuff, because the volume expansion of the intubated cuff is limited by the tracheal wall. The compliance of the portion of cuff that contacts with the tracheal wall is dictated by the properties of the tracheal wall, thereby causing a drastic reduction of compliance.

Studies in vitro[6, 7] and in vivo[4] have demonstrated that nitrous oxide diffuses into the air-inflated tracheal tube cuff and thus increases cuff volume and pressure. The rate of nitrous oxide diffusion varies inversely with cuff thickness and directly with the partial pressure gradient of nitrous oxide across the cuff membrane.[7] Also, the larger the volume of air in the cuff, the more nitrous oxide diffuses into the cuff to equilibrate the partial pressure gradient.

This study included two kinds of low-pressure tracheal tube cuffs, American Hi-Lo cuff and Shiley Low Pressure cuff. Both cuffs are made of polyvinylchloride but have different thicknesses and residual volumes. Thickness of the cuff wall and residual volume are 0.033 mm and 19.2 ml, respectively, for American Hi-Lo cuffs, and 0.135 mm and 6.9 ml, respectively, for the Shiley Low Pressure cuffs.[7] Due to the fact that the American Hi-Lo cuff is thinner and has a large residual volume compared to the Shiley Low Pressure cuff, the increase in intracuff pressure will be faster and more prolonged. This was demonstrated in the present study.

An in vitro study by Bernhard and colleagues[7] showed the rate of diffusion of 100% nitrous oxide into an air-inflated American Hi-Lo cuff was almost twice as fast as the rate of diffusion into a Shiley Low Pressure cuff. Stanley[4] reported an in vivo study that indicated that the minimum sealing pressure of both cuffs increased about 5-fold after 2 hours of intraoperative use of 60% nitrous oxide. Also, the intracuff pressure is known to be equal to the tracheal wall pressure in the large-volume, low-pressure cuff.[3] These reports as well as the present study demonstrate that low-pressure cuffed tracheal tubes do not protect against high tracheal wall pressure when nitrous oxide is administered.

Serious complications caused by overinflating cuffs during anesthesia are not well authenticated, except for airway obstruction due to a herniated cuff[8,9] and collapse of the lumen of the tracheal tube.[10] Homi and associates[11] reported that there was an abrupt increase in the degree of pallor of the tracheal mucosa at tracheal wall pressures between 30 and 40 mm Hg. Dobrin and colleagues[12] showed that blood flow in the tracheal mucosa decreased to 20% to 40% of control value with high-pressure cuffs, but almost no change was observed with low-pressure cuffs at the minimum sealing pressure.

In two studies silent regurgitation of stomach contents into the upper airway during endotracheal anesthesia occurred in 58 of 472 patients (12.3%)[13] and 22 of 152 patients (14.5%).[14] In four of the 58 and none of the 22 patients, the regurgitated dye passed the inflated tracheal tube cuff. Bernhard and associates[15] reported that when the intracuff pressure was controlled at 19 mm Hg, none of 21 patients whose tracheas were intubated with the American Hi-Lo Tracheal Tube aspirated dye placed on the tongue; however, six of 17 patients intubated with Portex Blue Line tracheal tubes aspirated at the same intracuff pressure. Pavlin and colleagues[16] reported a case in which intracuff pressure of Lanz tracheal tube was controlled at about 15 mm Hg. Repeated tracheal aspiration of blood occurred during spontaneous breathing but ceased when IPPV was applied. The explanation given was that when the large-volume cuff was inflated in the trachea, an overly large cuff tended to form longitudinal foldings. Spontaneous breathing and asynchronous breathing during mechanical ventilation generate negative pressure under the cuff and create a hydrostatic pressure gradient favoring tracheal aspiration along the fold. Pavlin et al recommended a small diameter cuff that can seal the trachea at low inflation pressures without making longitudinal foldings.

The minimum intracuff pressure required for an adequate tracheal seal has not been established for most brands of low-pressure cuffed tracheal tubes. However, Cross[17] claimed that it is unnecessary to have a tracheal wall pressure greater than the peak airway pressure. According to a report by Carroll,[18] tracheal mucosal pressure can be kept at 15 mm Hg during exhalation, to prevent aspiration without mucosal ischemia, when the trachea is intubated with a large-volume, low-pressure cuffed tracheal tube. The 20 mm Hg intracuff pressure of both American Hi-Lo and Shiley tubes appears to be adequate for IPPV and to prevent tracheal aspiration. Most patients in this study received IPPV in the horizontal position, which may help to prevent movement of regurgitated materials down into the lungs when and if it occurred.

In summary, a simple "Tracheal Tube Cuff Pressure Stabilizer" which can easily be assembled with materials readily available in the operating room area is described. The design was evaluated on 100 anesthetized patients endotracheally intubated with either American Hi-Lo or Shiley Low Pressure Cuffed tracheal tubes. Overinflated cuffs, either by intention or by diffusion of nitrous oxide into the air-containing cuff, rapidly, reliably, and automatically corrected to a predetermined pressure in cases in which TTCPS was used. When the TTCPS was bypassed, intracuff pressure rapidly increased. The TTCPS appears to be a valuable tool in preventing high tracheal wall pressure caused by an overinflated tracheal tube cuff.

## REFERENCES

1. Wu WH, Lim IT, Simpson FA, et al: Pressure dynamics of endotracheal and tracheostomy cuffs. Crit Care Med 1:197–202, 1973
2. Dobrin PB, Goldberg EM, Canfield TR: The endotracheal cuff: a comparative study. Anesth Analg 53:456–460, 1974
3. Crawley BE, Cross DE: Tracheal cuffs: a review and dynamic pressure study. Anaesthesia 30:4–11, 1975
4. Stanley TH: Nitrous oxide and pressures and volumes of high- and low-pressure endotracheal tube cuffs in intubated patients. Anesthesiology 42:637–640, 1975
5. Stanley TH, Foote JL, Liu WS: A simple pressure-relief valve to prevent increases in endotracheal tube cuff pressure and volume in intubated patients. Anesthesiology 43:478–481, 1975
6. Stanley TH, Kawamura R, Graves C: Effects of nitrous oxide on volume and pressure of endotracheal tube cuffs. Anesthesiology 41:256–261, 1974
7. Bernhard WN, Yost LC, Turndorf H, et al: Physical characteristics of and rates of nitrous oxide diffusion into tracheal tube cuffs. Anesthesiology 48:637–640, 1975
8. Ward CL, Gamel DM, Benumof JL: Endotracheal tube cuff herniation: a cause of delayed airway obstruction. Anesth Analg 57:114–116, 1978
9. Johnson JT, Maloney RW, Cummings CW: Tracheostomy tube: cuff obstruction. JAMA 238:211, 1977
10. Perel A, Katzenelson R, Klein E, et al: Collapse of endotracheal tube due to overinflation of high-compliance cuffs. Anesth Analg 56:731–733, 1977
11. Homi J, Notcutt W, Jones JJ, et al: A method for comparing

endotracheal cuffs: a controlled study of tracheal trauma in dogs. Br J Anaesth 50:435–443, 1978

12. Dobrin P, Canfield T: Cuffed endotracheal tubes: mucosal pressure and tracheal wall blood flow. Am J Surg 133:562–568, 1977
13. Blitt CD, Gutman HL, Cohen DD, et al: "Silent" regurgitation and aspiration during general anesthesia. Anesth Analg 49: 707–713, 1970
14. Turndorf H, Rodis ID, Clark TS: "Silent" regurgitation during general anesthesia. Anesth Analg 53:700–703, 1974
15. Bernhard WN, Cottrell JE, Sivakumaran C, et al: Adjustment of intracuff pressure to prevent aspiration. Anesthesiology 50: 363–366, 1979
16. Pavlin EG, VanNimwegan D, Hornbein TF: Failure of high-compliance low-pressure cuff to prevent aspiration. Anesthesiology 42:216–219, 1975
17. Cross DE: Comparison of tracheal cuffs (correspondence). Br J Anaesth 51:69–70, 1979
18. Carroll R: Evaluation of tracheal tube cuff designs. Crit Care Med 1:45–46, 1973

---

## Comparison of EEG and Carotid Stump Pressures

The correlation between carotid stump pressures and the results of intraoperative EEG monitoring were examined retrospectively for 289 carotid endarterectomies performed in 204 patients. A decision to place a temporary shunt during carotid endarterectomy was made entirely on the basis of intraoperative EEG monitoring. Evidence of ischemia on intraoperative EEG monitoring developed in 6% of the total series despite a stump pressure of greater than 50 mm Hg. The degree of disagreement between stump pressure and EEG varied according to clinical category. In those endarterectomies performed for completed stroke, all cases requiring shunting had stump pressures less than 50 mm Hg. In those cases performed for symptoms of vertebral basilar insufficiency, however, 77% of the cases requiring an intraoperative shunt had stump pressures greater than 50 mm Hg. A review of the complication rate in the various study groups indicates that the use of intraoperative EEG is a useful indicator of cerebral ischemia during carotid endarterectomy, regardless of stump pressure. *(Kelly JJ, Callow AD, O'Donnell TF, et al: Failure of carotid stump pressures: Its incidence as a predictor for a temporary shunt during carotid endarterectomy. Arch Surg 114:1361–1366, 1979)*

ANESTH ANALG
59:297-298, 1980

# Postoperative Venous Air Embolism

**Virgil M. Airola, MD***

Venous air embolism can precipitate cardiac arrest if it is of sufficient size to decrease cardiac output seriously. The presence of a central venous pressure (CVP) catheter and a low CVP predispose a patient to the development of a venous air embolism should the catheter somehow become open to air. The following case illustrates a situation in which this occurred.

## Case Report

A 56-year-old, 60-kg woman with a history of chronic renal failure underwent a gastric antrectomy-vagotomy because of partial gastric outlet obstruction resulting from severe peptic ulcer disease. On the day before surgery dialysis was performed with a loss of 1 kg of body weight. Preoperatively her blood pressure ranged between 168/70 to 120/60 torr, serum potassium ($K^+$) was 3.9 meq/L, and hemoglobin was 8.0 gm/100 ml. Her anesthetic course was uneventful. The anesthetic agents were thiopental, halothane, nitrous oxide-oxygen, and curare. A CVP catheter was placed through the left external jugular vein to monitor the CVP. The catheter could not be seen on the postoperative chest x-ray. During the 5-hour operation the patient received 900 ml of 5% dextrose in half-normal saline, 250 ml of normal saline, and two units of packed red blood cells. Estimated blood loss was 450 ml.

During the night following surgery the patient had several episodes of hypotension with the systolic blood pressure falling to 85 to 100 torr, associated with a pulse rate of 90 to 110 beats per minute and a CVP ranging between less than 0 to 1.0 cm $H_2O$. Each of these episodes responded to fluid administration. Two units of packed red blood cells, 250 ml of 25% albumin, 500 ml of normal saline, and 1000 ml of 5% dextrose in half-normal saline were administered in 16 hours. Measured fluid loss was confined to 400 ml through a nasogastric tube. There was no urinary output. The patient was kept at bedrest during the night.

At 6:00 a.m. the CVP was 0.5 cm $H_2O$ and at 6:30 a.m. her blood pressure was 120/60 torr with a pulse of 85 beats per minute. At 7:00 a.m. respirations were "noisy" at 24 per minute. She was medicated for pain with 6 mg of morphine intramuscularly. A blood specimen was drawn for hemoglobin (Hb) and electrolyte determinations (Hb, 9.2 gm/100 ml; $K^+$, 5.8 meq/L). At 7:15 a.m. the floor nurse heard the patient call for help. She found the patient supine, pale, with irregular respirations and a barely palpable carotid pulse. The CVP catheter, which had become separated from the tubing at the catheter hub, was reconnected. No blood was present on the bedsheets. The nurse did not attempt to aspirate blood through the CVP catheter or examine the catheter hub for air. She called the nearest physician, and cardiopulmonary resuscitation was instituted when he found no peripheral pulses.

Ventilation with 100% oxygen by mask failed to improve the patient's cyanosis despite obvious expansion of the chest and breath sounds in both axillae with each ventilation. The cyanosis persisted despite endotracheal intubation and continued adequate ventilation with 100% oxygen until the patient's hypotension began to resolve. No evidence of aspiration of gastric contents was found on laryngoscopy. A chest x-ray taken after resuscitation showed left lower lobe atelectasis which had been present on the immediate postoperative x-ray. An arterial blood sample taken during the period of cyanosis while the patient was being ventilated with 100% oxygen revealed pH 7.22; $Pa_{O_2}$, 101 torr; $Pa_{CO_2}$, 63 torr; $H_{CO_3^-}$ 27 meq/L; and base excess of −3.

With external cardiac massage palpable pulses returned and were well maintained without further assistance, but the patient remained hypotensive for 15 minutes. Initially the blood pressure of 70 torr systolic was attributed to a bradycardia, but correction of the 40 beats per minute pulse rate with intravenous atropine failed to improve the blood pressure. No other arrhythmias occurred. The heart was not auscultated during resuscitation; the presence or absence of a murmur remains unknown. The CVP was 12 cm $H_2O$ after correction of the bradycardia; yet only 300 ml of 5% dextrose in 0.2 normal saline had been administered during the arrest whereas during the night the administration of 150 ml of 25% albumin, one unit of packed red blood cells, and 250 ml of normal saline over a 3-hour period had raised the CVP from less than 0 to 4.5 cm $H_2O$. An hour after resuscitation the CVP was again 0.5 to 1 cm $H_2O$.

Four hours after the arrest, the patient's abdomen was reexplored when blood was found leaking from the abdominal wound. A small "ooze" in the retroperitoneal space near the pancreas was found with sufficient free blood and clot in the abdomen to explain a blood loss of 2 to 3 units.

Mild pulmonary edema by both x-ray and clinical criteria developed 6 to 8 hours after the resuscitation, but overly vigorous fluid therapy during a subsequent hypotensive episode and during the abdominal reexploration may have contributed to this. There was no evidence of sepsis as the basis for the patient's requirements of large volumes of intravenous fluids. There was no evidence of a myocardial infarction by sequential electrocardiograms.

---

* Fellow in Anesthesiology.

Received from the Department of Anesthesiology, S.U.N.Y. Upstate Medical Center, 750 East Adams Street, Syracuse, New York 13210. Accepted for publication December 6, 1979.

## Discussion

The signs and symptoms of a venous air embolism are generally nonspecific. Only changes in precordial Doppler ultrasound or a step-decrease in end-tidal $CO_2$ are specific signs for a pulmonary embolism of air or particulate material. A mill-wheel murmur may be the only specific sign of an air embolism. The diagnosis of venous air embolism in this patient is based on nonspecific clinical signs which resolved over a 15-minute period after her CVP catheter was open to air for several minutes. There is no evidence to support other possible causes, including myocardial infarction, pulmonary embolism of solid matter, aspiration, hemorrhagic shock, or sepsis.

The physiologic abnormalities exhibited by this patient during the cardiac arrest illustrate the physiologic derangements described by English et al[1] in experimental venous air embolism in dogs. Specifically, the abnormalities shown were increases in $Pa_{CO_2}$, alveolar-arterial oxygen difference ($A\text{-}a_{DO_2}$) and CVP, as well as hypotension and bradycardia. The prolonged cyanosis with a $Pa_{O_2}$ of 101 torr in our patient presumably reflected a low cardiac output with consequent oxygen desaturation of venous hemoglobin. The pulmonary edema[2,3] that developed may also have been related to air embolism though other causes may have been involved. The hypercapnia and large $A\text{-}a_{DO_2}$ associated with air embolism are due to a "redistribution" of a major portion of ventilation to areas of high ventilation-perfusion ratio ($\dot{V}_a/\dot{Q}$) and the coincident creation of areas of low $\dot{V}_A/\dot{Q}$ in the remaining portion of lung.[3] In addition, the time course for resolution of the hypotension and cyanosis in this case approached that described by Hlastala et al[3] for the resolution of experimental venous nitrogen embolism in dogs.

The importance of securing vascular lines well is emphasized by this case, as is the importance of closely following and appropriately treating a patient's fluid requirements. The major precipitating factor, however, was probably the development of a negative pressure gradient between the intrathoracic end of the CVP catheter and the end of the catheter which was open to the atmosphere. The negative intrathoracic pressure generated during inspiration with a partially obstructed upper airway or when a maximal inspiratory effort was made to call for help presumably resulted in a massive venous air embolism. This patient's continuing hypovolemia probably further increased the negative pressure gradient between the two ends of the catheter. Air probably entered the catheter when the catheter and CVP line came apart; no blood was present on the bedsheets.

Once a patient who has suffered air embolism has lost effective cardiac output, reestablishment of an adequate cardiac output is of paramount importance. If a cardiopulmonary arrest has occurred, as in this patient, implementation of basic life support is essential. Appropriate advanced life support can then be given. If an arrest has not occurred, however, what action should be taken? Alvaran et al[4] have shown that the left lateral decubitus position, external cardiac massage, and intracardiac aspiration of air via a venous catheter are all equally effective methods of resuscitation in terms of survival following air embolism in dogs. They also described, however, a shorter resuscitation time (2.7 minutes) with intracardiac aspiration of the air as compared to external cardiac massage (18.3 minutes) and a left lateral decubitus position (19.5 minutes). All of these maneuvers displace the right ventricular airlock from the right ventricular outflow tract allowing effective right heart filling and ejection of blood. External cardiac massage presumably pushes the airlock out of the heart into the pulmonary artery.

In summary, a patient appeared to suffer a large venous air embolism while supine in bed when her CVP line became disconnected at the catheter hub. Predisposing factors were hypovolemia and an increased negative intrathoracic pressure. The air embolism was large enough to precipitate a cardiac arrest. With the displacement of the right ventricular airlock by external cardiac massage the sequelae of a massive air embolism gradually resolved with the patient's return to her prearrest state.

### REFERENCES

1. English JB, Westenskow D, Hodget MK, et al: Comparison of venous air embolism monitoring methods in supine dogs. Anesthesiology 48:425–429, 1978
2. Still JA, Lederman DS, Renn WH: Pulmonary edema following air embolism. Anesthesiology 40:194–196, 1974.
3. Hlastala MP, Robertson HT, Ross BK: Gas exchange abnormalities produced by venous gas emboli. Respir Physiol 36:1–17, 1979
4. Alvaran SB, Touns JK, Graff TE, et al: Venous air embolism: comparative merits of external cardiac massage, intracardiac aspiration, and left lateral decubitus position. Anesth Analg 57: 166–170, 1978

ANESTH ANALG
59:299-300, 1980

# Delayed Horner's Syndrome following Obstetric Extradural Block

**Ronny Hertz, MD,***
**Claire A. Chiovari, MD,† and**
**Gertie F. Marx, MD‡**

Horner's syndrome has been reported as a complication of lumbar or sacral extradural block in parturients, occurring either in association with high sensory levels,[1-3] or immediately following administration of the test-dose.[2,4] We observed the development of a Horner's syndrome in a postpartum woman whose sensory analgesia had already worn off.

## Case Report

A 28-year-old secundipara requested extradural analgesia for relief of pain at 6-cm dilation of the cervix. The block was instituted at the L3-4 interspace. Following injection of a test dose of 2 ml of 2% chloroprocaine, a catheter was inserted cephalad approximately 2 cm beyond the needle tip and an additional 4 ml of chloroprocaine administered; sensory analgesia from T10 through L1 resulted. Forty minutes later, 5 ml of 0.375% bupivacaine was injected, after which the sensory level extended from T9 to L2. After another 30 minutes, the patient was ready for delivery. She was placed on the delivery table in the sitting position for administration of 8 ml of 3% chloroprocaine and remained sitting for 3 minutes. Perineal anesthesia was excellent (with the uppermost sensory level remaining at T9), and a healthy infant was delivered after 20 minutes with the mother in a semisitting position. Sixty-five minutes later, i.e., 115 minutes after injection of bupivacaine and 85 minutes after injection of 3% chloroprocaine, the woman sat up after being recumbent in the recovery room. Within 5 minutes, she complained of a "heavy" left eye. Immediate examination revealed left-sided ptosis and flushing of the left side of the face. Miosis developed in the left eye some 3 minutes later. External eye movements and function of cranial nerves were normal, as was sensation over face, trunk, perineum, and extremities; somatic motor function was also intact. Ptosis persisted for 12 minutes and anisocoria for 17 minutes. Thereafter, the patient had an uneventful course.

## Discussion

Horner's syndrome results from blockade of the sympathetic supply to pupil, levator palpebrae, conjunctiva, and face. One or more roots between the levels of C8 and T4 appear to be involved.[2] Owing to their thinness, sympathetic fibers are blocked at lower concentrations of local anesthetic than are sensory or motor fibers. Solutions placed in the extradural space are able to diffuse widely. Using epidurograms, Burn et al[5] showed that volumes exceeding 40 ml injected in the caudal or lumbar area consistently reached the upper thoracic or cervical region, whereas volumes of less than 20 ml did not. Albright[6] has suggested that doses of local anesthetic injected extradurally within 20 minutes of a previous dose are cumulative, whereas solutions administered more than 30 minutes after a preceding dose constitute a new injection. In our patient, all doses of local anesthetic had been injected in volumes of less than 20 ml and more than 30 minutes apart.

Previous reports of delayed Horner's syndrome following obstetric extradural analgesia were associated with use of bupivacaine or lidocaine, with or without epinephrine.[2] In a series of 20 parturients,[2] Horner's syndrome developed in one woman 100 minutes after injection of 17 ml of the anesthetic associated with a sensory level to T8 and in another patient 70 minutes after administration of 15 ml and a sensory level to T8; duration of the Horner's syndrome was 75 and 90 minutes, respectively. Although both chloroprocaine and bupivacaine were used in our patient, it is unlikely that the complication was related to the former drug as its duration of action is reliably short. Bupivacaine, on the other hand, "may occasionally have a slow, unpredictable spread of anesthetic effect..., result in spotty anesthesia, regress in 60 to 90 minutes, or continue to block higher spinal segments after the established block...."[6]

Previous explanations for the frequent appearance of Horner's syndrome in parturients have included reduction of potential volume of the extradural space by "increased extradural venous pressure produced

---

* Resident in Anesthesiology.

† Resident in Gynecology and Obstetrics.

‡ Professor of Anesthesiology.

Received from the Departments of Anesthesiology, and Gynecology and Obstetrics, Albert Einstein College of Medicine, Bronx, New York 10461. Accepted for publication December 6, 1979.

Reprint requests to Dr. Marx, Department of Anesthesiology, J 1226.

by inferior vena caval compression in the supine position and the haemodynamic effects of uterine contractions,"[3] and "driven labor with relatively high oxytocic dosage."[7] None of these factors was present in our patient. We have no ready explanation for the late onset of the complication. One may postulate that a minute amount of local anesthetic remained unbound in the thoracic extradural space and was propelled cephalad when the woman assumed the sitting position. In a personal communication, P. R. Bromage has observed that contrast medium injected into the thoracic extradural space of a sitting or standing patient spreads cephalad rather than caudad; he ascribes this to the increases in negative intrathoracic and positive intra-abdominal pressures in the upright posture.

Awareness of the possibility of delayed onset of Horner's syndrome, a benign transient complication of extradural block, will aid in allaying the patient's and family's anxiety. More importantly, the high sympathetic blockade with potential cardiovascular instability emphasizes the need for continued monitoring of vital signs in the obstetric recovery room.

## REFERENCES

1. Kepes ER, Martinez LR, Pantuck E, et al: Horner's syndrome following caudal anesthesia. NY J Med 72:946–947, 1972
2. Mohan J, Potter JM: Pupillary constriction and ptosis following caudal epidural analgesia. Anaesthesia 30:769–773, 1975
3. Evans JM, Gauci CA, Watkins G: Horner's syndrome as a complication of lumbar epidural block. Anaesthesia 30:774–777, 1975
4. Carrie LES, Mohan J: Horner's syndrome following obstetric extradural block. Br J Anaesth 48:611, 1976
5. Burn JM, Guyer PB, Langdon L: The spread of solutions injected into the epidural space. Br J Anaesth 45:338–345, 1973
6. Albright GA: Anesthesia in Obstetrics. Reading, MA, Addison-Wesley Publishing Co, 1978, pp 239–243
7. Bromage PR: Epidural Analgesia. Philadelphia, WB Saunders Co, 1978, pp 275, 588

ANESTH ANALG
59:301-303, 1980

# Timolol-Induced Bradycardia

**Jin W. Kim, MD* and**
**Porter H. Smith, MD†**

Timolol maleate (Timoptic, Merck Sharp & Dohme) is a recently introduced beta-adrenergic receptor blocking agent, the use of which is restricted to reduction of intraocular pressure (IOP) in patients with open-angle glaucoma.[1, 2] A relatively unknown beta-blocking agent to many anesthetists, timolol will undoubtedly be encountered with increasing frequency.

Beta-blocking agents should be administered systemically with caution in patients who have cardiac conduction defects greater than first degree A-V block. However, the topical use of the beta-blocking ophthalmic solution, timolol, has been shown to have minimal adverse systemic effects in normal volunteers.[3]

The following patient, who had cardiac conduction defects (left anterior hemiblock, first degree A-V block, and incomplete right bundle branch block), developed severe sinus bradycardia attributed to the use of timolol ophthalmic solution. Forty-eight hours after discontinuance of the timolol, the patient's normal heart rate was restored. Patients who have been using timolol opthalmic solution should be carefully screened preoperatively to prevent threatening bradycardia.

## Case Report

A 62-year-old male patient with open-angle glaucoma was scheduled for a sclerectomy filter operation under local anesthesia with an anesthetist in attendance. On admission his medical history revealed a number of hospitalizations over the previous 7 years, most of which were for cancer of the prostate with subsequent surgery and cystoscopies. During the last few hospitalizations, ECG tracings showed the conduction defects mentioned above, but his rhythm and rate had always been recorded as normal.

On this admission it was reported that he had been taking the following medications for his chronic glaucoma: pilocarpine, phospholine iodide, acetazolamide, epinephrine eye drops, and 0.5% timolol, the latter twice a day for more than a month. Blood pressure at the time of admission was 110/70 mm Hg with a regular pulse rate of 82 beats per minute. During the 24 hours before surgery, the pulse rate fluctuated between 42 and 84 beats per minute. This had not been evident on previous admissions. The present ECG was unchanged from that obtained at the time of his most recent admission, and physical examination was unremarkable.

The patient was premedicated with meperidine, 50 mg IM, and promethazine, 25 mg IM, 1 hour before the surgery. He arrived in the operating room somewhat restless with a blood pressure of 150/80 mm Hg and a pulse rate of 38 beats per minute. Atropine, 0.4 mg IV, increased the pulse rate to 78 beats per minute, and diazepam, 5 mg IV, produced satisfactory sedation. Eyelid and retrobulbar blocks were accomplished using 5 ml of 2% lidocaine with epinephrine (1:200,000) and 3 ml of 0.75% bupivacaine.

One hour after the beginning of surgery, the patient again showed restlessness, at which time his blood pressure increased to 160/90 mm Hg and his pulse gradually slowed to 38 beats per minute. Atropine, 0.2 mg IV, was given, which again restored the pulse to 80 beats per minute. Diazepam, 5 mg, and Innovar, 1 ml, were administered intravenously. The blood pressure rose to 230/120 mm Hg. Chlorpromazine, 2.5 mg IV, was given, and the pressure decreased to 160/100 mm Hg without a change in the pulse rate which remained at 80 beats per minute. One-half hour later the operation was completed without further need for sedation or atropine. Shortly after admission to the recovery room, the blood pressure was 140/90 mm Hg, and the pulse rate had decreased to 50 beats per minute. The patient was awake and relaxed. His blood pressure stabilized at around 110/70 mm Hg, but his pulse rate decreased further to 40 beats per minute.

At this point his preoperative ECGs were again reviewed. The previously noted first degree A-V block, incomplete right bundle branch block, and left anterior hemiblock persisted unchanged. Postoperative ECGs showed no changes except for a bradycardia of 38 beats per minute. The cardiology consultant recommended the use of a temporary pacemaker. In reviewing the chart again, it was noted that the patient had experienced episodes of bradycardia starting with use of timolol eye drops. It was speculated that beta-blocking effects of this drug in conjunction with the anesthetic medications were responsible for the persistent bradycardia. The use of a pacemaker was deferred while

---

* Assistant Administrative Director, Department of Anesthesia, Massachusetts Eye and Ear Infirmary; Instructor in Anaesthesia, Harvard Medical School, Boston.

† Chief, Department of Anesthesia, Massachusetts Eye and Ear Infirmary; Assistant Clinical Professor of Anaesthesia, Harvard Medical School, Boston.

Received from the Department of Anesthesia, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, Massachusetts 02114. Accepted for publication December 12, 1979.

Reprint requests to Dr. Kim.

the patient was carefully monitored by ECG. Timolol was discontinued.

The following day the patient's blood pressure remained at approximately 110/70 mm Hg with a pulse rate of 40 beats per minute. Otherwise, he was doing well. Almost 48 hours after discontinuation of the timolol, his pulse rate was between 68 and 80 beats per minute and remained in this range until his discharge from the hospital 1 week later.

## Discussion

Beta-adrenergic receptor antagonists, clinically introduced more than a decade ago, have proven effective in the treatment of cardiac arrhythmia, angina pectoris, and systemic hypertension.[4] Some also reduce normal and elevated intraocular pressure following oral, intravenous, and topical administration.[1-3, 5-8]

The ability of timolol maleate opthalmic solution, a beta$_1$- and beta$_2$-receptor blocker having no intrinsic sympathomimetic activity nor membrane stabilizing activity, to decrease IOP was recognized in normal volunteers.[3] The mechanism of action of timolol in reducing IOP is not known but appears to be a reduction of aqueous formation.[9] Timolol, paradoxically, even reduced IOP when given topically in patients responding to sympathomimetics with a reduction in IOP. Concomitant administration of timolol with epinephrine seems to enhance reduction of IOP in many patients with glaucoma, although its mode of action is unknown.[10, 11] Timolol is presently the beta-blocker of choice for management of increased IOP in patients with open-angle glaucoma and is widely used for this purpose.[11] The systemic use of beta-blockers is contraindicated in patients with congestive heart failure, bronchial asthma, marked sinus bradycardia, second or third degree A-V block, S-A block, sinus arrest, cardiogenic shock, and allergic rhinitis.[12] Timolol, as a beta-blocker is no exception to these contraindications due to possible systemic absorption, although timolol has been claimed to have minimal adverse systemic effects when used as topical ophthalmic solution.[3, 10, 11, 13] Katz et al[3] reported no clinically significant decreases in systemic or diastolic pressure or in heart rate after three successive weekend applications of timolol ophthalmic solution in normal volunteers.

However, McMahon et al[14] in their study of 165 patients (280 eyes) with various types of glaucoma who had been taking timolol for 3 months or more found adverse effects involving one or more organ systems in 38 (29%) of the patients after timolol was added to their glaucoma therapy. Side effects related to cardiovascular system included bradycardia, palpitations, hypotension, and syncope. Eight patients were symptomatic, but 39% of all patients had asymptomatic decreases in pulse rate. Syncope was reported by three patients.[14] Other serious side effects of timolol eye drops which have been reported include exacerbation of bronchial asthma[15] and worsening of congestive heart failure with bradycardia.[16]

Our patient had cardiac conduction defects greater than first degree A-V block and, therefore, timolol was relatively contraindicated. However, advantages represented by the ability to control IOP in difficult glaucoma cases with the use of timolol may outweigh the disadvantages of potential adverse effects on the cardiovascular system, especially when other antiglaucoma drugs may have proven ineffective.

Despite reported clinical cases of adverse effects, timolol represents a major advance in the medical therapy of glaucoma with a minimum of systemic side effects[17] and, therefore, will be encountered with increasing frequency.

The extent to which systemic absorption may occur after a prolonged topical use of timolol and the magnitude of the subsequent adverse effects are presently not clear, but it is important for anesthetists to remember that beta-blocking agents other than propranolol are being used clinically for noncardiovascular purposes. Patients receiving timolol ophthalmic solution for treatment of open-angle glaucoma should be carefully screened preoperatively for possible effects of timolol on the cardiac conduction system. In the presence of severe bradycardia or heart blocks, timolol should be discontinued before elective surgery until normal heart rate is restored.

In our case, 48 hours after discontinuation of timolol ophthalmic solution, heart rate returned to normal. If the clinical situation does not permit discontinuation of timolol, atropine, isoproterenol, and a temporary pacemaker should be available perioperatively.

### REFERENCES

1. Zimmerman TJ, Kaufman HE: Timolol, a beta-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol 95:601–604, 1977
2. Boger WP III, Puliafito CA, Steinert RF, et al: Long-term experience with timolol ophthalmic solution in patients with open-angle glaucoma. Trans Ophthalmol Soc UK 85:259–267, 1978
3. Katz IM, Hubbard WA, Getson AJ, et al: Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. Invest Ophthalmol 15:489–492, 1976
4. Goodman LS, Gilman A: $\beta$-Adrenergic blocking agents, in The Pharmacological Basis of Therapeutics. Fifth edition. New York, Macmillan Publishing Co, Inc, 1975, pp 547–552
5. Phillips CI, Howitt G, Rowlands DJ: Propranolol as ocular hypotensive agent. Br J Ophthalmol 51:222–226, 1967

6. Cote G, Drane SM: The effect of propranolol on human intraocular pressure. Can J Ophthalmol 3:207-212, 1968
7. Bonomi L, Steindler P: Effect of pindolol on intraocular pressure. Br J Ophthalmol 59:301-303, 1975
8. Elliot MJ, Cullen PM, Phillips CJ: Ocular hypotensive effects of atenolol (Tenormin, I.C.I.): a new β-adrenergic. Br J Ophthalmol 59:296-300, 1975
9. Coakes RL, Brubaker RF: The mechanism of timolol in lowering intraocular pressure in the normal eye. Arch Ophthalmol 96: 2045-2048, 1978
10. Zimmerman TJ, Gillespie JE, Kass MA, et al: Timolol plus maximum-tolerated antiglaucoma therapy. Arch Ophthalmol 97:278-279, 1979
11. Katz IM: Beta-blockers and the eye: an overview. Ann Ophthalmol 10:847-850, 1978
12. Chung EK: Management of cardiac arrhythmias, propranolol, in Principles of Cardiac Arrhythmias. Second edition. Baltimore, Williams & Wilkins, 1977, pp 575-577
13. Sonntag JR, Bundley GO, Shield MB, et al: Timolol and epinephrine, comparison of efficacy and side effects. Arch Ophthalmol 91:273-277, 1979
14. McMahon CD, Shaffer RN, Hoskins HC, et al: Adverse effects experienced by patients taking timolol. Am J Ophthalmol 88: 736-738, 1979
15. Jones FL Jr, Ekberg NL: Exacerbation of asthma by timolol. N Engl J Med 301:270, 1979
16. Britman NA: Cardiac effects of topical timolol. N Engl J Med 300:566, 1979
17. Karlin KM, Olander K, Mandelkorn RM, et al: More about timolol. N Engl J Med 301:944-945, 1979

---

## Gas Gangrene Associated with Radial Artery Catheterization

Fatal *Clostridium perfringens* septicemia occurred in an adult diabetic admitted with severe ketoacidosis, complicated subsequently by congestive heart failure and respiratory failure. Swelling and cyanosis was first observed at the insertion site of a radial artery catheter, and subcutaneous crepitus was also noted in the area. The insertion sites of two venous catheters were not affected. Subcutaneous crepitus was also detected in the left calf. The patient developed profound shock and died 10 hours after the localized infection was first observed. *Clostridium perfringens* was isolated from blood cultures. The author suggests that strict observation of established infection control procedures when indwelling intravascular devices are used should prevent this type of hospital-acquired infection. *(Rose HD: Gas gangrene and Clostridium perfringens septicemia associated with the use of an indwelling radial artery catheter. Can Med Assoc J 121:1595-1596, 1979)*

*See also—Meakins JL: Infection associated with radial artery catheters. Can Med Assoc J 121:1564-1565, 1979*

ANESTH ANALG
59:304-307, 1980

# Cardiopagus in Neonatal Thoracopagus Twins: Anesthetic Management

**Edmond C. Bloch, MB, ChB, FFARCS,* and Joannes H. Karis, MD†**

During the last three decades, descriptions of the anesthetic management of conjoined twins for separation surgery have appeared in the literature, and reviews have been presented by Keats et al[1] and Jarem et al.[2] We have not been able to find a description of the management of anesthesia for the separation of thoracopagus twins with multiple cardiac anomalies and a vascular communication between the two hearts. We think that the latter anomaly is aptly described by the term cardiopagus; we present this report to describe our unusual case and the unusually early intervention that was forced upon us.

The female twins were the product of an unremarkable 39-week gestation in a 36-year-old gravida 8, para 9. Because of a transverse presentation, cesarean section was decided upon, during which the unexpected conjoined twins were delivered. Both infants had Apgar scores of 8/8 at 1 and 5 minutes, and after initial stabilization were transferred to our institution within a few hours. The combined weight was 5440 gm; baby A appearing to be slightly larger than baby B.

Persistently low arterial oxygen tensions ($Pa_{O_2} = 40$ mm Hg, $F_{IO_2} = 1.0$) led to cardiac catheterization on the 2nd day for evaluation of possible congenital cardiac defects. Angiographic studies revealed that the left atria were joined by what appeared to be a myocardial bridge containing a vascular channel. In addition to this, baby A had a ventricular septal defect, an atrial septal defect, a patent ductus arteriosus, and severe pulmonary atresia. Baby B had tricuspid atresia, common atria, and a small patent ductus arteriosus (Figure). The infants appeared to have a common liver with separate biliary systems. The intestinal and renal systems were separate. The angiographic investigation was complicated by severe metabolic acidosis which necessitated, among other measures, ventilatory assistance. To this end, awake endotracheal intubation was performed in both infants without muscle relaxants and without difficulty using 3-mm i.d. tubes, despite their face-to-face position. Separate ventilators were used to provide mechanical ventilation for each infant, and the endotracheal tubes remained in situ for the rest of their management.

The angiographic studies in baby A indicated that pulmonary perfusion was totally dependent upon flow through the ductus arteriosus, and then via two rather small pulmonary arteries to the pulmonary circulation. In order to increase pulmonary flow and thereby improve the arterial oxygen tension, it was decided to administer prostaglandin $E_1$, since this hormone maintains the patency of the ductus arteriosus.[3, 4] Initially, this was attempted by means of an infusion via a peripheral vein on the dorsum of the left hand at a dose of 0.1 μg/kg/min, but this had no effect as judged by measurements of $Pa_{O_2}$. A catheter was then threaded retrogradely through the femoral artery into the aorta until its tip lay at the point in the aorta at which the ductus arteriosus arose. Infusion of prostaglandin $E_1$ at the same dose level made it possible to reduce the $F_{IO_2}$ from 1.0 to 0.4 while maintaining arterial oxygen tensions in the range of 40 to 50 mm Hg. Because of circulatory failure in baby B, a dopamine infusion (14 μg/kg/min) was started on day 6.

It became apparent that drugs given to one infant often worsened the condition of the other and that neither infant was improving despite intensive multisystem support. By the 9th day, it was decided that surgical separation offered the only chance of survival.

On the afternoon before surgery, the anesthesiologists, surgeons, and pediatricians conferred at length concerning the status of the infants, and a coordinated plan of action was decided upon. A rehearsal was conducted in the operating room, during which every step of the proposed procedure was simulated so that each person knew what was expected of him and how he was to coordinate his activities with others.

---

* Assistant Professor of Anesthesiology.

† Professor of Anesthesiology.

Received from the Department of Anesthesiology, P.O. Box 3094, Duke University Medical Center, Durham, North Carolina 27710. Accepted for publication December 24, 1979.

Reprint requests to Dr. Bloch.

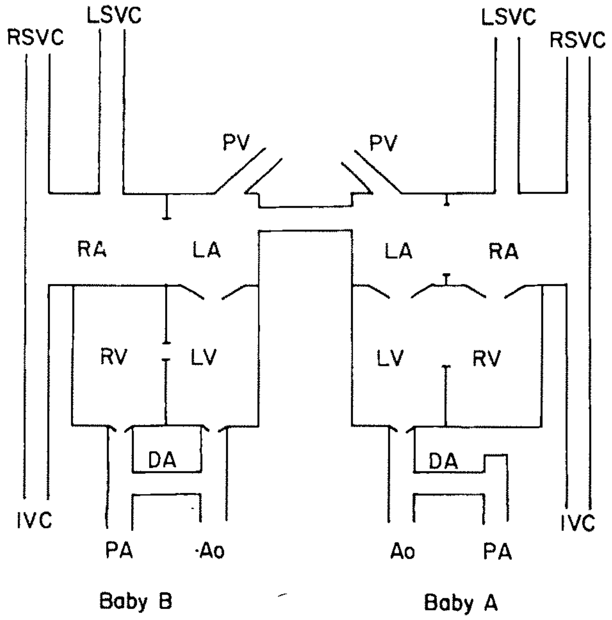


FIGURE. Diagrammatic representation of cardiovascular anomalies. RSVC, right superior vena cava; LSVC, left superior vena cava; IVC, inferior vena cava; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; DA, ductus arteriosus; PA, pulmonary artery; AO, aorta; PV, pulmonary vein.

## Separation Procedure

There were two anesthesia teams. Each consisted of a senior anesthesiologist, an assistant, and an anesthesia technician. An additional anesthesiologist was present to coordinate activities, to ensure the availability of drugs and blood, and to supervise the recording of data.

In both infants the right temporal artery had been catheterized for monitoring of blood gas tensions and arterial pressure in the intensive care nursery. The left femoral veins had also been catheterized for central venous pressure monitoring. On arrival in the operating room the electrocardiograms (lead II), electroencephalograms, and intra-arterial and central venous pressures were displayed on two separate polygraph strip recorders. Temperatures were monitored by means of esophageal probes.

Anesthesia was induced with a mixture of 50% $N_2O/O_2$ administered via the endotracheal tubes from separate anesthesia machines. We used a Bain circuit for baby A and the Rees modification of Ayres T-piece for baby B, these being the preferences of the individual anesthesiologists concerned. Both infants were manually ventilated throughout surgery and, by frequent reference to arterial blood gas tensions, a moderate degree of respiratory alkalosis was maintained. We anticipated and indeed found this to be useful in maintaining an acceptable arterial pH in the face of, at times, quite alarming metabolic acidosis which we managed with sodium bicarbonate in appropriate doses. (Baby A received 18 meq of sodium bicarbonate in five divided doses, and baby B received 24 meq in three divided doses.)

The pharmacokinetics of the situation was complex. In view of our experience with therapeutic agents in the intensive care unit, we anticipated that there would be some degree of cross-circulation. In addition both infants were somewhat edematous, making prediction of drug dosages more difficult. We gave 0.15 mg of pancuronium intravenously to baby B, and 14 minutes later we noted that, while the effect on baby B was considerable, there was very little effect on baby A. We therefore decided each team would manage pancuronium and other drug requirements for their respective patients.

Separation was commenced by opening the abdomen. The common liver was divided, using a tourniquet and electrosurgical hemostasis. Major blood loss occurred at this time.

Following separation of the diaphragms, the common pericardial sac was opened and this revealed two hearts with a bridge of tissue 2 cm in length and 4 cm in diameter joining the two left atria in their lower posterior aspects. Just before division was attempted, baby B developed ventricular fibrillation. This responded to 0.2 mg of intracardiac epinephrine and dc defibrillation using 10 watt seconds. Thereafter, separation was completed uneventfully. At this time another operating table with warming blanket and sterile drapes was moved up and baby B was transferred to it without disruption of anesthetic management and monitoring. Closure of the defect in this baby, commencing with the abdomen, proceeded well until the last few sutures were being placed to approximate the edges of the defect over the heart. These sutures were tied under some considerable tension and this resulted in acute cardiac tamponade. The sutures were rapidly removed and construction of a tent-shaped prosthesis of Silastic-reinforced Dacron sheeting to cover the defect proved to be the solution to this problem.

In baby A, following separation, the problem of inadequate pulmonary flow was dealt with by means of a prosthetic graft anastamosis 4 mm in diameter between the pulmonary artery and the aorta. After this, $Pa_{O_2}$ rose from 55 to 91 mm Hg, the $FI_{O_2}$ at this time being 0.5. During closure of the abdominal defect, it was noted with concern that the liver appeared cyanotic, but no anatomical reason for this was evident. Repair of the abdominal and chest defects in this child necessitated the use of a sheet of Silastic and Teflon felt to obtain closure.

During separation, it was impossible to know which infant was losing blood volume and though we had facilities for measuring blood loss by gravimetric and colorimetric methods, we found this to be of no practical value. The replacement of blood loss could only be managed by reference to the arterial and central venous pressures in each infant. In order to have better control of filling pressures in baby A, a left atrial catheter was inserted after separation. This infant received a total of 425 ml of fresh whole blood, and baby B received 190 ml of fresh whole blood. The infants were in the operating room for nearly 7 hours, during which time baby A received a total of 1.25 mg of pancuronium and baby B a total of 0.77 mg of pancuronium. Since both were in unstable condition at the conclusion of surgery, we decided instead of reversing the relaxant to resume mechanical ventilation postoperatively.

Both patients were taken to the intensive care nursery in reasonable but by no means satisfactory condition, each requiring intensive pharmacologic and ventilatory support. They had stormy postoperative courses with problems arising from hemorrhage, hypotension, acidosis, renal and hepatic failure, and disseminated intravascular coagulopathy. Baby A died 24 hours after surgery and baby B 2 days thereafter. Postmortem examinations confirmed the anatomical defects that had been diagnosed preoperatively. The primary cause of death was considered to be congestive cardiac failure resulting in pulmonary, renal, and hepatic insufficiency.

## Discussion

We found the following points to be particularly important in an anesthetic management of these two patients:

1. Thorough preoperative discussion with surgical and pediatric colleagues in the relaxed atmosphere of a conference room provided a detailed description of the anatomical and functional anomalies and an appreciation of the medical status of the infants.

2. A detailed rehearsal of the entire procedure, going through each step from transportation from the nursery to separation of the infants and, as in our case, the movement to a separate operating table. Each member of the team knew exactly what his responsibilities were and thus confusion was avoided.

3. The use of color coding for all vascular lines, monitoring leads, apparatus, records and personnel as advocated by Furman et al.[5] We used two completely separate anesthesia machines and monitoring systems.

4. The use of central venous and intra-arterial pressures as a guide to blood loss replacement, and as continuous indicators of cardiovascular function and of tamponade.

5. The availability of laboratory facilities near the operating room for the rapid determination of arterial blood gases, hematocrit and electrolytes.

6. The application of all possible measures to maintain normothermia. Despite all our efforts (room temperature 76 F, circulating warm water mattresses, heated humidified gases, warmed intravenous fluids and blood) baby B arrived in the intensive care unit with a rectal temperature of 34 C, and temperature only reached normal levels 8 hours later.

7. Restriction of people in the operating room. Only essential personnel were admitted, but despite this, overcrowding in the operating room was a notable burden.

8. Placement of all required arterial and venous lines prior to the transport of the infants to the operating room. In general, it is easier to maintain normothermia while placing these lines in the environment of an intensive care nursery; the anesthesiologist will, upon arrival in the operating room, then be able to direct his attention to the well-being of the infants, rather than becoming involved in technical manipulations.

9. Plans to communicate with the parents and the media. Each institution will have its own particular circumstances; in our hospital a nurse was assigned solely to communicate with and support the parents, and a physician was designated to communicate with the media. Hospital security staff not only assured us of unhampered movement from the nursery to the operating room and back through tightly controlled corridors, but also prevented unauthorized entrance to the operating rooms.

10. In view of the large amounts of sodium bicarbonate we found necessary to control metabolic acidosis, we would in the future be more cognizant of the hazards of the sodium load and hyperosmolarity; since our patients were being ventilated, tris(hydroxymethyl)aminomethane (THAM) might have been preferable to sodium bicarbonate.

11. We feel that it is important to establish an airway and be able to control ventilation in both patients before relaxant drugs are given to either infant. This is because the effect on the second infant may not be predictable since the direction of cross-circulation may vary from minute to minute.

In summary, our experience in dealing with these neonatal thoracopagus twins with cardiopagus emphasizes the necessity for thorough advance discussions between surgeons, anesthesiologists, and pediatricians, rehearsal in the operating room, and meticulous attention to the pharmacologic responses of both infants to drugs given to one.

## REFERENCES

1. Keats AS, Cave PE, Slataper EL, et al: Conjoined twins: a review of anesthetic management for separating operations, in The National Foundation, Birth Defects Original Article Series: Vol III (1). Edited by D. Bergsma. Baltimore, Williams & Wilkins, 1967, pp 80–88
2. Jarem BJ, Flewellen EH, Tyson KRT, et al: Anesthetic management for separation of conjoined twins. Anesthesiol Rev 4:17–22, 1977
3. Weir EK, Matison RE, Losman E, et al: Prostaglandin $E_1$ in infants with pulmonary atresia. S Afr Med J 54:700–702, 1978
4. Eliott RB, Starling MB, Neutze JM: Medical manipulation of the ductus arteriosus. Lancet 1:140–142, 1975
5. Furman EB, Roman DG, Hairabet, et al: Management of anesthesia for surgical separation of newborn conjoined twins. Anesthesiology 34:95–101, 1971

ANESTH ANALG
59:308-310, 1980

# A Quantitative Neuromuscular Blockade Monitor

**John P. Karis, Larry W. Burton, PhD,* and Joannes H. Karis, MD†**

Introduction of muscle relaxants into clinical anesthesia has enabled the anesthesiologist to provide his surgical colleagues with operative conditions which were difficult to achieve without the use of these drugs. Unfortunately, the administration of muscle relaxants is complicated by a large difference in drug sensitivity among patients. For example, Katz[1] found that 0.1 mg/kg of *d*-tubocurarine produced approximately 50% reduction in twitch height in the majority of patients, but 7% of the patients were totally paralyzed while 6% were unaffected. Clinical signs including the "feel of the bag" generally are inadequate guides for either the dose of relaxant needed to provide adequate surgical relaxation or for recognition of the return of normal neuromuscular transmission. Stimulation of a peripheral nerve and observation of the resulting mechanical or electrical activity of the muscle can give a direct measurement of the degree of neuromuscular blockade. Botelho[2] concluded from a study in patients with myasthenia gravis and in partially curarized patients that measurement of the mechanical activity was more accurate than use of the electromyogram. As early as 1958, Christie and Churchill-Davidson[3] suggested the use of a nerve stimulator during procedures in which muscle relaxants were used for more than endotracheal intubation.

Although methods exist to measure and thus to quantitate the twitch tension caused by nerve stimulation, the traditional instrumentation is relatively expensive, cumbersome, and time consuming to apply. As a result, some anesthesiologists depend upon the visual observation of the hand movement, while others do not consider that the benefits derived from the use of a nerve stimulator justify the application of stimulating electrodes. Many anesthesiologists prefer the use of a train-of-four stimuli at 2 Hz as popularized by Ali et al.[4] Since the second, third, and fourth twitch are progressively more depressed by nondepolarizing neuromuscular blocking agents, one can better evaluate the depth of a neuromuscular block with a train-of-four stimuli than with single stimuli.

Anesthesiologists need an apparatus that gives an accurate quantitative measure of the degree of neuromuscular block, yet requires little time to apply and is not influenced by the operation of other instruments. We have designed and tested an instrument that meets these criteria.

## Methodology and Circuit Description

The quantitative neuromuscular blockade (QNB) monitor is portable and battery operated. It consists of two parts: a nerve stimulator and an apparatus that quantitates the resulting twitch tension. Referring to Fig. 1, its operation can be described as follows.

Power is supplied from a 12-volt rechargeable battery, utilizing a dc-dc converter and subsequent linear regulation (A). Three timing oscillators (B) run continuously to provide a 2 Hz train-of-four timing signal, a 50-Hz tetanus signal, and a 30-, 60-, 120-, or 180-second stimulus interval timing signal. Logic circuitry (C) generates 0.2-msec stimulus pulses at appropriate intervals. The pulses are amplified by the electrically isolated output stage (D) to provide a voltage suitable for stimulation of the ulnar nerve. If desired, a 50-Hz tetanic stimulus can be delivered.

Mechanical twitches of the patient's hand are sensed from pressure changes in the air-filled bag being gripped by the patient (E). Peak pressures corresponding to maximum twitch tension are detected and stored by the pulse analysis circuitry (F). The ratio of the maximum response of the first train-of-four pulse to a reference (beginning of case) value and the ratio of the maximum response of the fourth pulse to the first pulse (T4/T1) are expressed as percent on two digital displays (G).

Use of the instrument in a typical case is as follows: a surface ECG electrode is applied over the ulnar nerve at the elbow and another over the ulnar nerve proximal to the wrist. The patient's hand with the fingers slightly flexed is inserted in a transparent plastic box with the palmar surface contacting an air-filled rubber bag inflated to a pressure of approxi-

---

* Assistant Medical Research Professor of Anesthesiology.

† Professor of Anesthesiology.

Received from the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina 27710. Accepted for publication December 26, 1979.

Reprint requests to Dr. Karis.

mately 30 mm Hg. Train-of-four stimuli are given every 15 seconds while constantly increasing the amplitude of the stimulus. Eventually, the reading of the meter marked "Percent of Original" will reach a maximum, indicating that a supramaximal response has been obtained. Stimulus amplitude is then further increased to ensure that the stimulus is well above the supramaximal value. The "Reference Set" knob is adjusted next so that the "Percent of Original" meter indicates 100% and the stimulus repetition is switched to the desired rate. Operation of the device is totally automatic from this point on with the percent of the original twitch as well as the T4/T1 ratio being displayed continuously.

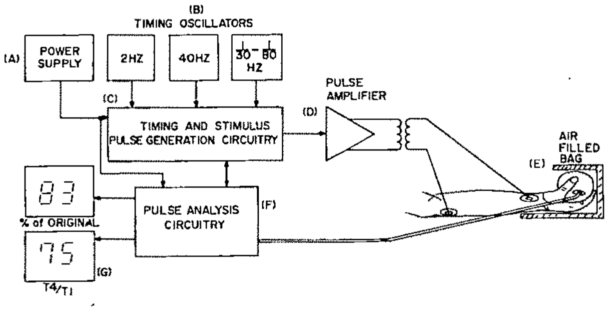


FIG 1. QNB circuit block diagram.

The device has been used in a variety of orthopedic and general surgical procedures in which neuromuscular blocking agents were required. In six patients, in whom both arms were accessible and with the patient's informed consent, one arm was connected to the QNB monitor and the other to a conventional system, consisting of a Grass force transducer and polygraph.

## Results

The progression of a neuromuscular block as measured with both the QNB monitor and the conventional method is plotted in Fig 2. The twitch tension is indicated as a percentage of the control following the administration of *d*-tubocurarine. This graph was chosen because of the relative lack of sensitivity of this 74-kg patient. He received 42 mg of curare before the neuromuscular blockade became 80% effective; half this amount is the average dose needed for a patient of his size to produce a block of this degree. The information thus obtained was very helpful during the management of this case. Fig 3 shows the T4/

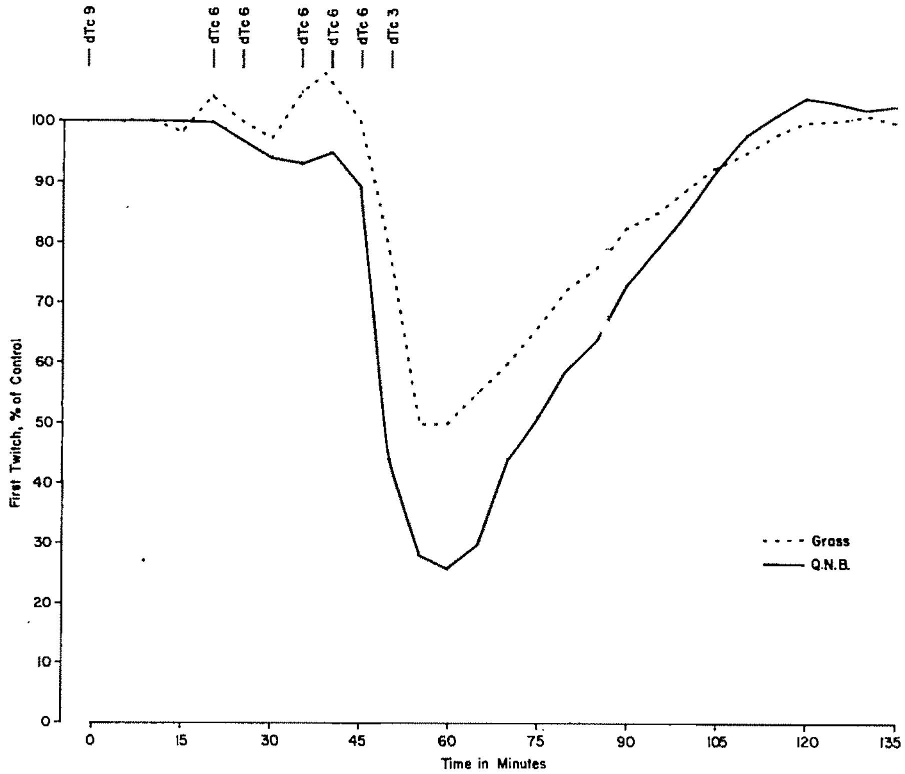


FIG 2. Changes in twitch tension as percentage of control evoked by the first stimulus of a train-of-four stimuli as calculated from a recording using a force displacement transducer (broken line) and as plotted from values obtained with the QNB monitor (solid line).

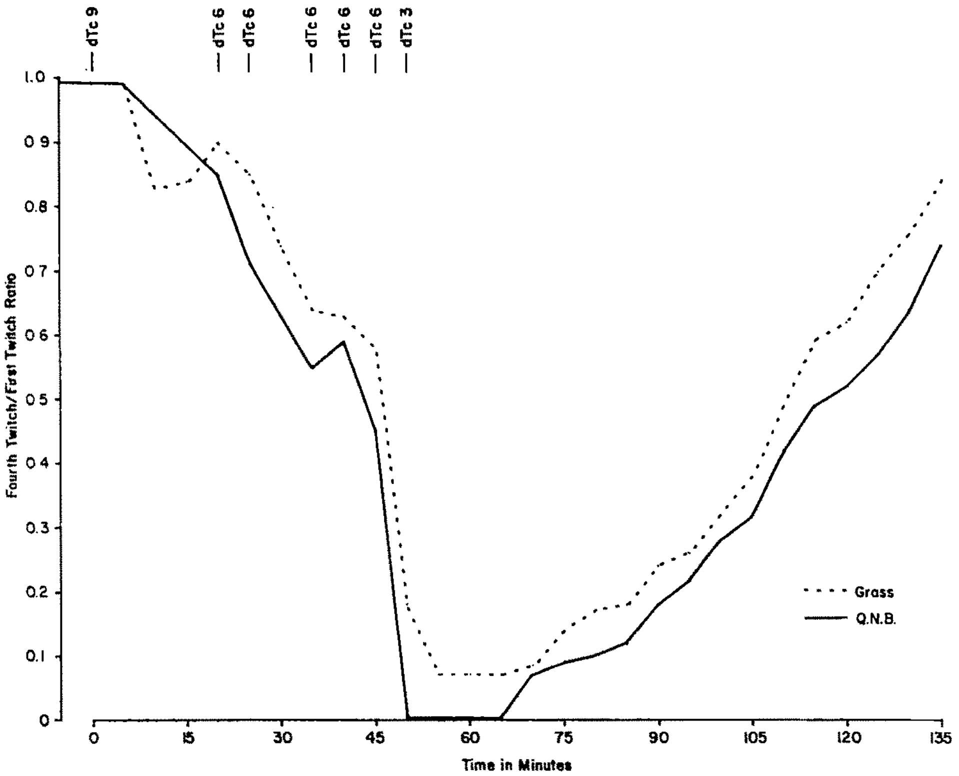


FIG 3. Ratios between heights of fourth and first twitch responses as calculated from a recording made with a force displacement transducer (broken line) and plotted from values obtained with the QNB monitor (solid line).

T1 ratio measured in the same patient during the same case. Although small differences between the tracings are visible, they are of little clinical importance and may be due to a difference in sensitivity to the drug in each arm rather than the different methodology. In all patients in whom comparative measurements were made, the percentage of twitch tension indicated by the QNB monitor correlated well with percentages calculated from values obtained with the conventional method.

We found that artifacts caused by positioning and surgical manipulation were less pronounced with the QNB monitor than with the conventional Grass recording.

## Discussion

A portable, noninvasive, inexpensive device for quantitative monitoring of neuromuscular blockade is described. This device is simple to use and is suitable for routine use in anesthesia. It is suggested that the routine quantitative monitoring of neuromuscular blockade will allow the anesthetist to titrate more accurately the dose of both neuromuscular relaxants and antagonists according to the needs of the individual patient. In addition, the device provides a useful educational tool for instruction in safe administration of neuromuscular blocking and reversal agents. We anticipate that the device will become available commercially at a reasonable cost in the near future.

## REFERENCES

1. Katz RL, Katz GJ: Clinical considerations in the use of muscle relaxants, in Muscle Relaxants. Edited by R Katz. New York American Elsevier Publishing Co, 1975, pp 313–334
2. Botelho SY: Comparison of simultaneously recorded electrical and mechanical activity in myasthenia gravis patients and in partially curarized normal humans. Am J Med 19:683–696, 1955
3. Christie TM, Churchill-Davidson HC: The St Thomas Hospital nerve stimulator in the diagnosis of prolonged apnoea. Lancet 1:776, 1958
4. Ali HH, Utting JE, Gray C: Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 42:967–977, 1970

ANESTH ANALG
59:311-313, 1980

# Postoperative Alopecia

**Kita D. Patel, MD,* and
E. O. Henschel, MD†**

Postoperative alopecia due to intraoperative pressure on the scalp has been described as a minor reversible complication of anesthesia.[1] Review of the literature[2-6] shows that postoperative pressure alopecia is most likely to occur after lengthy anesthesia associated with hypotension, blood loss, or continued pressure over an area of the scalp. The present case describes development of temporary alopecia with none of the precipitating factors reported in the literature which resulted from pressure of a soft foam "doughnut" used to rest the head of a patient during a lengthy anesthetic.

## Case Report

A 15-year-old white girl was scheduled for an elective left reduction mammoplasty and right mastopexy. Preoperative evaluation showed the patient to be in excellent health. She gave a past history of spinal meningitis as a child with complete recovery. She had no previous surgery and was not on any medications. Physical examination, in addition to the mammary findings, revealed only a soft systolic murmur, heard best at the apex. Laboratory data were within normal limits.

The patient was premedicated with Innovar (1.5 ml) and atropine (0.6 mg) intramuscularly. Anesthesia was induced with thiopental (450 mg) and, after 3 mg of *d*-tubocurarine, succinylcholine (100 mg) was given and the trachea intubated with a size 36 oral endotracheal tube. Anesthesia was maintained with $N_2O$, $O_2$, and halothane.

The patient was placed in a 40° Fowler's position with both arms at her side. Her waist-length hair was covered with a paper cap and the head positioned over a soft foam "doughnut."

Anesthesia was uneventful during the 6¼-hour operation. Specifically, there was no hypotension. Estimated blood loss was 400 ml. Five percent dextrose in lactated Ringer's solution (1050 ml) was given during the procedure.

On her follow-up visit to the clinic, a month after surgery, the patient complained of excessive hair loss. She reported that two bald spots on the occipital area were noted by a friend. The loss of hair was not associated with pain, tenderness, swelling, itching, exudation, or scaling.

On examination (Fig 1), two symmetrical areas 3 x 2 cm and 3 x 5 cm in size resembling alopecia areata were noted. The bald areas, identical in shape, followed the outline of the foam "doughnut" on which the patient's head rested during the surgical procedure (Fig 2). Reexamination 2 months after anesthesia revealed short stubs of hair. Complete regrowth of hair occurred in 6 months.

## Discussion

Postoperative pressure alopecia, though a minor and self-limiting complication of general anesthesia,[1] is disturbing to both patient and physician. Temporary loss of hair unaccompanied by atrophy or scarring may occur from a number of etiologic factors (Table).[2-13]

Abel[6] has reported a series of 16 cases of reversible postoperative alopecia. The majority of these patients had undergone lengthy gynecologic procedures in the Trendelenburg position with associated hypotension. In the immediate postoperative period, 50% of the patients complained of pain, swelling, or serous exudation and crusting in the area of scalp upon which the head rested during the operation. Central vertex was the most common area to be affected, although alopecia also involved the occipital and parietal areas in some patients. Alopecia appeared about the 15th day (range of 3 to 28 days) following anesthesia. Complete regrowth occurred in all cases within 120 days. The authors advised the use of foam doughnuts under the head as one of the measures for prevention of this complication.

Gormley and Sokoll[14] in 1967 reported a case of permanent alopecia resulting from the use of a head strap with a face mask during the 6¼-hour anesthetic. During this time the head strap was not loosened or detached and permanent alopecia resulted.

The head of a normal adult weighs about 2.8 kg. This weight usually rests on the same scalp area when the patient is in the supine position. The pressure on the scalp may be increased in certain positions, especially the Trendelenburg position.[2] The resultant pressure-induced ischemia may cause temporary cessation of follicular activity leading to loosening and

---

* Assistant Professor, Acting Chief, Department of Anesthesiology, Mount Sinai Medical Center, Milwaukee.

† Late Professor and Chairman, Department of Anesthesiology, The Medical College of Wisconsin; Director, Department of Anesthesiology, Milwaukee County Medical Complex; and Chief, Anesthesiology Services, Veterans Administration Center, Wood, Wisconsin.

Received from the Department of Anesthesiology, Mount Sinai Medical Center, 950 North Twelfth Street, Milwaukee, Wisconsin 53201. Accepted for publication December 24, 1979.

Reprint requests to Dr. Patel.

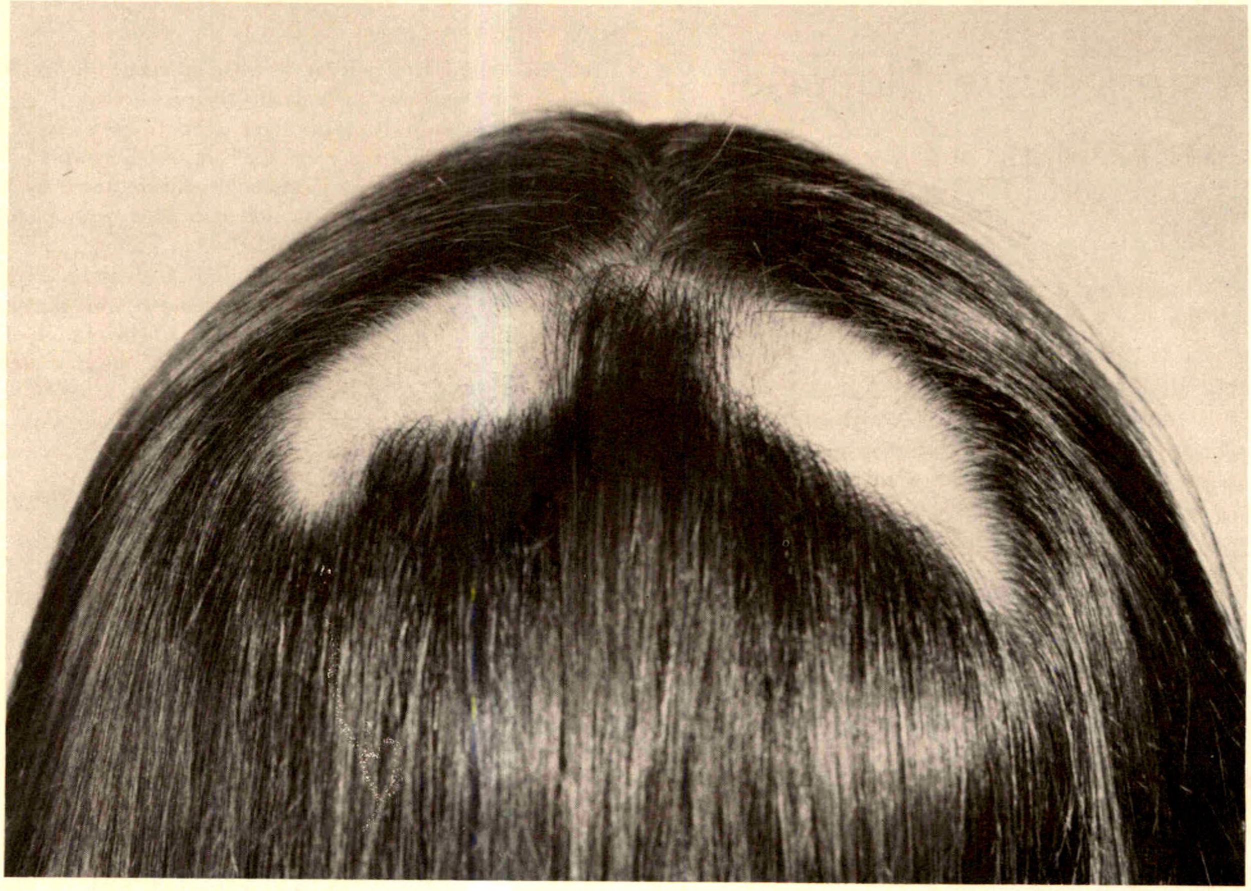


FIG 1. Two symmetrical areas of postoperative pressure alopecia seen 60 days after anesthesia.

depilation. Comparable pressure-induced ischemia probably explains the case of permanent alopecia reported by Gormley and Sokoll.[14] By holding the anesthesia face mask, the dependent force is increased by the anesthesiologist's hand.[2]

Scalp ischemia secondary to pressure could be aggrevated by blood loss and vasoconstriction or by hypotension in further circulatory insufficiency of the skin.[2]

Abel and Lewis[2] found pressure-induced alopecia to be associated with obliterative vasculitis in experimental animals.

It is of interest, that our patient developed alopecia even though her hair was protected with a cap and her head placed on a soft foam rubber "doughnut." The Fowler's position places the maximum pressure on the base of the occiput, not the dorsum, where the alopecia was noted. Moreover, the patient was not hypotensive during the prolonged anesthetic.

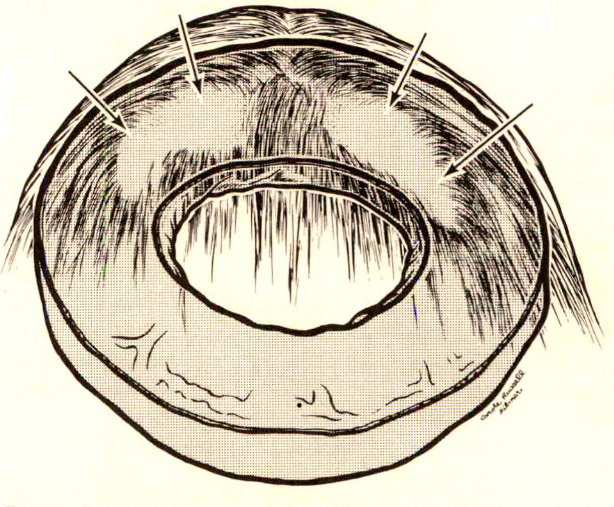


FIG 2. Areas of alopecia followed the outline of the foam rubber "doughnut" on which the head of the patient rested for 6¼ hours.

Our patient developed relatively sudden onset of symptomless loss of hair. The differential diagnosis included concomitant and purely coincidental occurrence of alopecia areata. However, in alopecia areata the spontaneous regrowth is often associated with depigmented hair, or faulty stubs of hair, the so-called "exclamation point" hairs.[15] Microscopic examination

**TABLE**

**Etiologic Factors of Alcopecia**

| | |
|---|---|
| 1. Traction | Acute: trichotillomania<br>Chronic: "Pony tail" alopecia and alopecia marginalis |
| 2. Chemicals | Dyes, bleaches, ammonium thioglycolate, chlorobutadiene |
| 3. Infection | *Staphylococcus aureus*; ringworm infection |
| 4. Drugs | Anticoagulants<br>Chemotherapeutic agents<br>Chlorpromazine<br>Excessive doses of vitamin A |
| 5. Miscellaneous | Alopecia areata<br>Prolonged febrile illnesses<br>Systemic lupus erythematosus<br>Severe cachexia<br>Endocrine disorders |
| 6. Trauma | Acute trauma—blow to the scalp<br>Prolonged pressure |

of the area confirms the diagnosis as the underlying process is inflammatory.

In our patient, the clinical picture did resemble alopecia areata, but as biopsy of the area of alopecia was refused by the patient, the concomitant occurrence of alopecia areata cannot be ruled out.

The occurrence of postoperative alopecia can be avoided by intermittent repositioning of the head, by minimizing areas of unavoidable pressures, and by avoiding hypotension.[6]

In summary, a case of postoperative pressure alopecia is reported, where none of the usual contributing factors were present. A soft foam "doughnut" was used to stabilize the head during the procedure and yet postoperative alopecia occurred.

## REFERENCES

1. Riding JE: Complications of general anaesthesia. Br J Anaesth 47:91-101 1975
2. Abel RR, Lewis GM: Post-operative pressure alopecia. Arch Dermatol 81:72-78, 1960
3. Wintrobe MM: Harrison's Principles of Internal Medicine. Sixth edition. New York, McGraw Hill Book Co, 1966, pp 294-295
4. Oya M: Post-operative alopecia. IRYO 16:1-7, 1962 (Japanese)
5. Fischer R, Bircher J, Reich T: Der Haarausfallnach Antikoagulierender Therapie. Schweiz Med Wochenschr 83:509-511, 1953
6. Abel RR: Post-operative (pressure) alopecia. Anesthesiology 25:869-871, 1964
7. Aaronson CV: Etiologic factors in traction alopecia: South Med J 62:185-186, 1969
8. Morgan NV: Traction alopecia. Br Med J 2:115-117, 1960
9. Reiches AJ, Lane CW: Temporary baldness due to cold wave preparation: thioglycolate preparations. JAMA 144:305-306, 1950
10. Abel RR, Lewis GM: Postoperative (pressure) alopecia. Arch Dermatol 81:79-80, 1960
11. Thomson NB, Estrellado R: Occurrence of alopecia after open heart surgery. Arch Surg 85:892-896, 1962
12. Muneyuki M, Kurimoto S, Araki Y, et al: Anaesthesia and heart surgery. 1. Minor complications with special reference to post operative alopecia. Jpn J Anesthesiol 15:71-76, 1966
13. Lee JA, Atkinson RS: A Synopsis of Anaesthesia. Seventh edition. Bristol, John Wright and Sons Ltd, 1973, p 829
14. Gormley T, Sokoll MD: Permanent alopecia from pressure of head strap. JAMA 199:157-158, 1967
15. Shelly WB: Consultation of Dermatology. Philadelphia, WB Saunders Co, 1972, pp 14-19

# letters TO THE EDITOR

## USP Oxygen Standards

To the Editor:

The letter to the Editor by Bassell et al (Anesth Analg 58:441–442, 1979) raised a question as to the adequacy of the quality standards for oxygen as provided for in the United States Pharmacopeia. The rationale for such an implication was based on two premises: (1) In a gas chromatogram they detected an unidentified peak which they concluded was some hydrocarbon. (2) USP standards do not account for all possible contaminants. Proof of this was that if oxygen USP were to assay at the minimum (99.0%), and at the maximum 300 ppm carbon dioxide, 10 ppm carbon monoxide, and 5 ppm oxides of nitrogen, there could possibly be 9685 ppm unaccounted for. From these premises they concluded that oxygen USP could be contaminated with toxic and even lethal amounts of hydrogen cyanide, benzene, and carbon tetrachloride.

Such unfounded scare tactics must be countered with facts. First, compendial standards cannot possibly exclude every possible contaminant in every product. The aim is to test for and limit those contaminants that are *likely* to occur as a result of the manufacturing, processing, and packaging processes. This is recognized in the "General Notices" in the USP: "... it is manifestly impossible to include in each monograph a test for every impurity or adulterant that might be present.... Tests suitable for detecting impurities the presence of which is inconsistent with good pharmaceutical practice ... should be employed in addition to the tests provided in the individual monograph."

Furthermore, the USP monograph on oxygen specifically states: "Containers used for oxygen must not be treated with any toxic, sleep-inducing, or narcosis-producing compounds, and must not be treated with any compound that will be irritating to the respiratory tract when the oxygen is used."

Oxygen USP is generally produced cryogenically by the liquefaction of air. It normally contains 99.5% to 99.7% oxygen, 0.3 to 0.5% argon, 5 to 50 ppm of methane, and little else. USP XX (released January 2, 1980) requires that the label indicate whether or not the oxygen has been produced by the air-liquefaction process, and further such oxygen is exempt from the requirements for limits of carbon dioxide and carbon monoxide because the process eliminates them. There is no limit for argon because it is inert and harmless at these levels.

The authors did not identify or quantify the peak they observed by gas chromatography. They apparently had no evidence that it was any of the three hypothetical contaminants; more than likely it was methane, which is not removed by the air-liquefaction process. Brannon et al (J Assoc Off Anal Chem 59:1404, 1979) of the Food and Drug Administration, using infrared spectrophotometry, detected methane at levels of approximately 20 to 40 ppm in three samples of oxygen USP. Such small quantities are unobjectionable under conditions in which oxygen is customarily employed.

William W. Wright, PhD
*Senior Scientist*
*Drug Standards Division*
*United States Pharmacopeia*
*Rockville, MD 20852*

## Purity of Oxygen, USP

To the Editor:

The letter of Bassell et al on "Purity of USP Medical Oxygen," (Anesth Analg 58:441–442 1979) has drawn attention to the absence of clear guidance for users on the amounts of which impurities are likely to be present in a cylinder of oxygen.

There presently exist two separate standards: (1) the USP, which requires that oxygen shall contain not less than 99.0% by volume of oxygen, and (2) the Compressed Gas Association pamphlets G4, "Oxygen," and G.4.3 "Commodity Specification for Oxygen." The G.4.3 document specifies eight grades of oxygen, of which grade A, containing 99.0% $O_2$, and grade D, containing 99.5% $O_2$, satisfy the USP requirements. Grade E, containing 99.5% $O_2$ and defined low levels of hydrocarbons is the specification used for welding! Grade F at 99.99% $O_2$ and grades G and H at 99.995% $O_2$ are normally used only for analytical purposes.

Although oxygen produced by the fractional distillation of compressed air must be of at least welding grade at the distillation plant, much of it is supplied to the medical consumer in small cylinders which are transfilled from larger ones by local oxygen distributors (Stanford Smith, Task Force Chairman, USP Monograph for Medical Gases, Compressed Gas Association, personal communication). These smaller cylinders are evacuated by vacuum before filling with oxygen; however, a certain amount of nitrogen will be present so the percentage of oxygen in the cylinder will be less than the 99.5% plus purity supplied by the producer. The simple Orsat test specified in the USP must be carried out by the distributor before releasing cylinders to medical users in order to satisfy FDA requirements. The CGA Commodity Specification for Oxygen specifies a gas chromatograph and other sophisticated apparatus that may be used to determine the quantities of inert gases, hydrocarbons, methane, ethane, ethylene, acetylene, $CO_2$, CO, nitrous oxide, and halogenated refrigerant or solvent that may be present.

The Compressed Gas Association has published a similar pamphlet G7.1, "Commodity Specification for Air," which is also American National Standard Z86.1-1973 and in pamphlet G7, "Compressed Air for Human Respiration," they explain which grades of compressed air are suitable for use in industry, fire fighting, or general respiratory use and which types are suitable for sports diving to a depth of 125 feet.

It is clear to me that the present problem with standards for oxygen could readily be solved if the CGA documents on oxygen were reviewed for publication as an ANSI Standard with an explanatory pamphlet similar to the one on "Compressed Air for Human Respiration," to define which grades of oxygen are suitable for which purpose. This would clearly indicate to the research worker, welder, or physician treating a patient the grade of oxygen they should use. For example, I am sure that Bassell et al would be much happier consulting the Compressed Gas Association's "Commodity Specification of Oxygen" which clearly indicates that in, for example, grade E (normally used for welding), the maximum levels of hydrocarbons permissible are methane, 40 ppm; ethane, 3 ppm; ethylene, 0.2 ppm; and acetylene, 0.05 ppm. Once these documents become an official American National Standards Institute Standard it will be a simple matter for the USP to reference the ANSI documents so that research workers can be guided to the grade of $O_2$ and the more precise analytical methods that their work might require.

I sincerely hope that the Compressed Gas Association will take the initiative in publication of such a useful standard.

Leslie Rendell-Baker, MD
*Vice Chairman*
*Committee Z79 ANSI*
*Veterans Administration*
*Loma Linda, California 92357*

# book REVIEWS

### Controversy in Anesthesiology, by J. E. Eckenhoff, Philadelphia, W. B. Saunders Co., 1979, 312 pp, $22.00.

Debate enjoys a venerable reputation in education and Dr. Eckenhoff has used the technique effectively by soliciting two authoritative essays propounding opposing views on a number of controversial issues in anesthesia practice. The text contains approximately 20 essays with editorials, principally by the author whose professional stature and experience afford a perspective uncommon among anesthesiologists.

The topics debated include halothane hepatitis; the effect of anesthetics on reproduction; sterilization of anesthetic equipment; deliberate hypotension; tracheal intubation in parturients and in infants; anesthesia for coronary artery bypass operations; acupuncture; intermittent positive pressure breathing; intra-arterial monitoring; the training and supervision of nurse anesthetists, including their use of regional anesthesia; and the responsibility for patient care in intensive care units.

On some issues Dr. Eckenhoff argues for gradual, timely adaptation to evolutionary change and thereby reconciles dissimilar views. He urges more immediate solutions for other issues, however, and proposes efficacy as justification for modifying practice. In the case of anesthetic effect upon reproduction and regarding intermittent positive pressure breathing, the urgency seems prompted by an awareness of an increasingly regulated, litigious society striving for cost containment and demanding quick answers to seemingly unanswerable questions. While few of us will be dissuaded from our personal biases, most should come away better informed about many facets of these particular issues and perhaps with the focus of our professional orientation sharpened. If criticism of the book is to be levied, it is toward the uneven quality of the presentations. Some of the adversarial papers seem to lack conviction in the counterpoint of the controversy the authors were asked to present. This limitation notwithstanding, the book deserves a careful reading by residents and practicing anesthesiologists. This much is not an issue for debate.

Alan D. Sessler, MD
Professor of Anesthesiology
Mayo Medical School
Rochester, MN

### Shock Trauma Manual, by W. Gill and W. B. Long. Baltimore, Williams & Wilkins Co., 1979, 296 pp, $18.00.

In 1971, one in four Americans was injured, 115,000 fatally. Eleven million required one or more days in a hospital, and 40,000 had long-term disability. Recognition of the need for improved prehospital care resulted in the EMT/Paramedic movement. But as Gill and Long point out, "A sophisticated systems approach of triage, communication, and transport is of little avail if medical expertise of the highest order does not await the victim's arrival." And it does not. This manual aims to increase the effectiveness of the trauma team—surgeon leader, surgeon assistant, anesthesiologist, and nurses—by stressing organization and preplanning. The manual arises from the authors' experience at the Maryland Institute for Emergency Medicine. It is "a pragmatic guide to the logistics of evaluation and resuscitation of a patient with multiple and potentially critical injuries." "(It) may help bridge the gap between education and experience." Not an easy assignment!

The book can be divided into three parts: (1) There is an 85-page theoretical discussion of aggressive diagnosis and therapy for the dynamically deteriorating multitrauma patient. There is still much to be discovered and the authors indicate areas of controversy. However, on the basis of their clinical experience, they recommended early intubation, minimal crystalloid, packed-cell reconstituted with 250 ml of plasma protein extract, and steroids, if necessary. The essential role of the anesthesiologist on the trauma team is stressed; but it is doubtful that an anesthesiologist helped write or proofread the book. For example, the importance of basic airway control, the oral and nasal airway, the full stomach, and cricoid pressure are not mentioned and, on page 23, nasal airway and nasal intubation are confused. (2) There is a collection of 135 pages of Trauma Algorithms (with Dr. William Sacco) which are an outstanding contribution to learning and practice. There are obvious disadvantages to the algorithm approach—each patient is unique, perception is important in diagnosis, etc; however, they do provide the score to orchestrate the trauma team. They give an overview, help organize knowledge, and they are a potent source of stimulation and continuing education. In this manual, lack of adequate numbering of the algorithms makes cross-reference cumbersome. In practice, they should be displayed on the wall of the resuscitation room for ease of reference. (3) There is a Guide to Organization (with Mary Kellog, RN) and a Technical Appendix (illustrated by T. L. Holt), both of which are useful reference sources especially for the smaller unit. There is room for improvement. The diagrams appear to be drawn by a talented amateur. They lack clarity, due to insufficient discrimination of surfaces and allusions to the third dimension. More specifically, the intubation diagram shows the blade incorrectly positioned on the dorsum of the tongue. The instructions for insertion of the Swan-Ganz catheter are confusing and need a pressure tracing illustration. Many authorities do not agree with bilateral subclavian vein catheterization, etc.

But overall, this manual is an ambitious undertaking which fills a practical need in a short space. The presentation is less than ideal, there are mistakes, and the authors offer controversial therapies; however, their message concerning the need to preplan and organize rapid and aggressive therapy for the victim of multiple trauma comes over loud and clear. Although this book is not written primarily for the anesthesiologist, it should be required reading for every resident. It will be a stimulus for those in practice.

Trevor Hughes, MD
Assistant Clinical Professor
of Anesthesia
Veterans Administration Hospital
Martinez, CA

---

## **Modern Hospital,** by E. Pütsep, London, Lloyd-Luke Ltd, 1979, 687 pp, $20.00.

*Modern Hospital—International Planning Practices* is an extensive presentation of the problems and attitudes involved in modern hospital design. It should prove to be an excellent introduction for the architect who is not yet initiated into the complex and often mystifying activities that compose the present-day hospital. Applicable world literature is referred to frequently and its detailed referencing makes this text a massive personal undertaking for its author, a Stockholm architect and writer whose stature is well recognized among hospital planners.

An anesthesiologist interested in hospital planning and construction will probably find this book difficult reading. The anesthesiologist could regard much of the book as pompous, philosophical, clumsily generalized, and even superficial, but occasional bits hidden throughout bear upon issues about which he as a planner must be knowledgeable even though the conclusions offered might not be agreeable to him. The bibliography is rewarding reading, and major parts of the book, such as the discussions of air-handling, infection, and lighting, are highly informative.

Mr. Pütsep makes interesting and valid points about poor information-sharing among architects worldwide regarding hospital planning and construction. He also describes computer programs that generate trivia disguised as guidelines. In each instance he offers positive conclusions which will assist the reader. At certain places in the text, he might be unwittingly reporting an opinion of a reference source in such a way as to inadvertently set an international standard; e.g., the statement on page 341 that every patient undergoing a general anesthetic should have an EKG applied as a monitor certainly would provoke enthusiastic counter-opinions from many sources and is hard to rationalize as a necessary item in an architectural text. The comment on page 539 that anesthesia be terminated postoperatively in an induction space adjacent to the operating room is thought provoking, as is the suggestion that recovery rooms have individual cubicles to reduce patient anxiety. Items of contention include the statement (p 600) that only obstetrical suites with more than 3000 deliveries per year merit anesthesia work rooms and the comment (p 634) that obtaining a preanesthetic physical examination and laboratory tests the day before, rather than 2 hours preoperatively, is "unnecessary."

Despite the fact that Mr. Pütsep's new text *Modern Hospitals* is not geared specifically to the anesthesiologist, it will doubtless prove to be a major addition to architectural literature and deserves praise. Its presence in the library should be known to anesthesiologists involved in hospital planning and construction and it should be used as an authoritative and helpful reference.

John T. Martin, MD
Professor of Anesthesiology
Medical College of Ohio
Toledo, OH

---

## **Nutritional Aspects of Care in the Critically Ill,** edited by J. R. Richards and J. M. Kinney, New York, Churchill Livingstone, 1977, 668 pp, $29.50.

This is a timely book, timely because the potential for saving lives and shortening postoperative convalescence through nutritional measures has been widely recognized only in the last decade. This volume provides both basic physiologic information and observations in particular clinical situations which will enable the incorporation of nutritional principles into the care of the surgical patient. Assessment of the risk of surgery and anesthesia, choice of optimum time, and preparation for surgery and care of the patient during the postoperative period will be facilitated by familiarity with information in this text.

Papers presented at a conference organized by the University Department Glasgow Royal Infirmary in honor of John E. Kinney, Professor of Surgery at the College of Physicians and Surgeons of Columbia University, New York, make up the 29 chapters. The first two chapters by S. M. Levenson and associates from the Albert Einstein College of Medicine and by Dr Kinney are comprehensive and authoritative accounts of the metabolic effects of starvation and of stress. Tribute is paid to the pioneering efforts of Sir David Cuthberton of the Royal Infirmary in Glasgow; his studies more than 40 years ago of fracture patients have been used to establish many of the principles that are verified and expanded in this volume.

Some quotes give the flavor of the contents of this volume. "The greater the energy stores of the body before injury, the better the prognosis for survival." "The late return of a normal work capacity in convalescence is related to the extent of breakdown of muscle protoplasm during the period of maximum catabolism in the flow phase after injury." "It is perhaps best after the initial shock phase to leave the room heating controls in the hands of the patient?" "... cells and tissues in the ill are in an inflationary situation with increased and perhaps rising energy costs of maintaining metabolic and ionic balance, with diminishing energy reserves within cells and a falling store of potential energy in membrane ion-gradients. *Provision of substrate must be a priority.*" "Many of the nonspecific responses—characteristic of most infectious diseases—are associated with the mobilization of body protein for the synthesis of those proteins necessary for the host's defense against the infectious organism and for the production of glucose to be oxidized as a source of energy."

Other chapters consider metabolic responses to infection, protein turnover in injury, rationale for glucose as a primary calorie source, respiratory function in the critically ill, nutritional support in liver failure, nutrition and cancer, use of intravenous hyperalimentation in malignancy and in sepsis, and nutrition in burns.

This volume is heartily recommended to the practicing anesthesiologist as a basic text for study and as a reference source.

C. F. Gastineau, MD
Professor of Medicine
Mayo Medical School
Rochester, MN

## **Coronary Heart Surgery,** edited by H. Roskamm and M. Schmuziger, Secaucus, NJ, Springer Verlag, 1979, 394 pp, $42.90.

Papers presented at the European Society of Cardiology, March 1978, are collected in this book. There is no effort to editorialize, edit, or explain. According to the editors, the papers were selected to stimulate controversy and to present wide viewpoints. As such, the book presents a cafeteria of approaches, opinions, and prejudices which make interesting reading for those curious about how others look at this topic, but the book provides little in-depth analysis.

Many of the papers read like basic made-simple presentations of techniques. Their authors rarely distinguish broadly accepted from locally adapted approaches, heightening the impression of confusion in the field. Some papers are presented in the guise of scientific studies with minimal control and methods slanted to confirm a preconceived conclusion or to prove a point already well established.

As at any such meeting, there are some presentations that clearly stand out from the rest, in interest and quality. Lister's article on tachyarrhythmias as an indication for cardiac surgery (p 141) presents a good electrophysiologic analysis of arrhythmias which will broaden the understanding of anesthesiologists who have some understanding of these principles. Kirk's diagrams and discussion on subendocardial versus epicardial infarction, and regional and collateral perfusion (p 196) will increase the depth of understanding of coronary perfusion. Bregman's description of a new pulsatile pump, which combines a conventional cardiopulmonary bypass apparatus with a modified balloon pump (p 211) may prove to be a workable answer to a long-standing problem. Clark's data on myocardial preservation using the calcium antagonist Nifedipine (p 249) exemplifies results obtained in using a new drug class that may achieve widespread application in this country in the near future.

For the practicing anesthesiologist the greatest merit of this book is its introduction and discussion of new pre-op, post-op, and intra-op medical and surgical approaches that may differ from more familiar personal or institutional approaches. The various American and European physicians appear to be unsure of each others' sophistication and awareness of their own techniques and so proceed by presenting basic rationale and discussion. Future meetings are bound to progress rapidly toward more esoteric and narrow discussions, but the uniqueness of this meeting saves what might have been a highly technical but loosely connected series of papers, by presenting an intelligible and basic overview of a growing and challenging area.

Lawrence M. Abrams, MD
Anesthesia Department
Texas Medical Center
Baylor College of Medicine
Houston, TX

## **Outpatient Surgery,** edited by R. C. Schultz, Philadelphia, Lea & Febiger, 1979, 470 pp, $48.50.

Richard C. Schultz, MD states that the purpose of this book is to describe how outpatient surgical facilities can function safely, how they can succeed, and how anesthesia and surgery can be performed in these units. This text accomplishes this stated purpose by drawing from the experiences of many anesthesiologists and surgeons who have been involved in outpatient surgery for several years. It is of note that a significant contribution was made by the anesthesiologists responsible for starting one of the first and most successful free-standing surgical centers, the Phoenix Surgicenter.

The book is divided into three sections with the first section devoted to organization of an outpatient surgical center. This section on organization discusses such things as scheduling, the significant cost-saving features of outpatient surgery, administration, personnel, as well as anesthetic techniques and recovery and discharge. Four of the six chapters in this section are authored by members of the Phoenix Surgicenter group. Consequently, the major portion of material presented is devoted to outpatient facilities that are independent of hospitals. Little mention is made of hospital outpatient facilities that share inpatient operating and recovery rooms other than to note the numerous disadvantages of such facilities.

The chapter devoted to anesthetic management describes those techniques preferred by anesthesiologists of the Phoenix Surgicenter. They note that children most often receive inhalational anesthesia with halothane and that approximately 45% undergo endotracheal intubation, thus dispelling the once-believed myth that endotracheal intubation is a contraindication to outpatient anesthesia. One brief section in the chapter on anesthetic management is devoted to anesthesia for oral surgery. This section, the only weak section in the book describes anesthetic techniques that most anesthesiologists would find unacceptable. The author is apparently an oral surgeon (his name is not included in the list of contributors), and he discusses the office use of anesthetic agents including not only barbiturates and narcotics, but also the potent inhalational agents such as halothane and enflurane. The author refers to the mortality rate of 1 per 432,000 dental anesthetics, a figure obtained from a survey of the Southern California Society of Oral Surgeons. He favorably compares this to a rate of 1 per 10,000 for inpatient tonsillectomy and adenoidectomy, apparently assuming that both procedures are similar in difficulty, risk, and postoperative problems. The author also discusses the administration of the anesthetic which requires three "team" members: the surgeon, the first assistant, and the head holder. It is not apparent from the discussion which member administers the anesthetic, although he states that the oral surgeon is responsible for the selection of the agent, and the head holder is responsible for the airway.

The second section of this book is devoted to discussion of specific outpatient surgical procedures with a chapter devoted to each surgical subspecialty. In describing the surgical procedures done in the outpatient setting, this section reassures reluctant surgeons that many surgical procedures once done only as inpatient procedures are now commonly done on an outpatient basis. In addition to a discussion of cases, the surgeon authors of some chapters discuss local and regional anesthetic techniques. References are made to the use of 2% lidocaine solutions for local nerve blocks, blocks in which a 1% lidocaine solution will suffice with less risk of nerve damage. In addition, "Boer Block" is described. It is presumed that the author is referring to the Bier block.

The final section of this book includes a chapter on legal aspects and a chapter on the financial considerations for outpatient surgery. The chapter on financial considerations is noteworthy; it is again written by the Phoenix Surgicenter group and it gives a great deal of insight into the needs and financial problems encountered in starting a free-standing surgical center.

In conclusion, with the exception of the section on anesthesia for outpatient oral surgery, this book is well written and a timely contribution to a rapidly growing field. The book is an excellent reference source for those engaged in outpatient anesthesia and surgery.

Stephen M. Brzica, Jr., MD
Assistant Professor
of Anesthesia
University of Minnesota
Director of Anesthesia
St. Paul Surgical Center
St. Paul, MN

---

## **Acute Care,** edited by B. M. Tavares and R. Frey, Secaucus, NJ, Springer-Verlag, 1979, 345 pp, $42.90.

*Acute Care* contains the Proceedings of the International Symposium on Acute Care held in Rio de Janeiro in 1977. To edit and, in turn, review a book of this type is no simple task, mainly due to lack of uniformity which is inherent in such a book.

The soft cover volume has been divided into 10 sections: (1) Metabolism in Critical Care Medicine; (2) Monitoring of the Critically Ill Patient; (3) Organization of Intensive Care; (4) Hematology and Coagulation; (5) Respiration; (6) Gastroenterology; (7) Cardiology; (8) Shock; (9) Infection, and (10) Side Effects of Drugs.

With this diversity of material, the editors perhaps could have been more rigid in the format and style of the different chapters. While some chapters represent "finalized papers" (i.e., 2.3); others are abstracts (i.e., 5.4); and others are unreadable summaries of preliminary research (e.g., 2.8). Also, the format of the chapters is not standardized, and in some articles the graphics and diagrams have legends in German with no English translations (i.e., 3.2).

The medical content of this book is as heterogenous as its editorial style. Under the name of acute medicine, it indicates emergency medicine, intensive care, as well as other subjects, such as "stabilization of the spine in vertebral tumors," and "traumas by means of spondylodesis with Harrington Rods and Bone Cement" which are hardly within the scope of acute medicine.

This book contains some interesting articles such as, "Cerebral Prognosis Determined During Cardiopulmonary Resuscitation," while others, most likely due to the abstract form, leave the reader without the whole message of the study.

Not being a comprehensive text in acute care, this volume may not satisfy the reader who wants a complete, current overview of the subject. However, it can be a useful experience for the "intensivists" who will find interesting and stimulating papers somewhere in the 60 chapters included.

Teruel de Campo, MD
Assistant Professor of
Anesthesiology and Surgery
Director, Surgical Intensive
Care Unit
University of Colorado
Medical Center
Denver, CO

---

# BOOK NOTE

## **1979 Year Book of Anesthesia,** edited by J. E. Eckenhoff, A. J. Bart, E. A. Brunner, H. S. Holley, and H. W. Linde, Chicago, Year Book Medical Publishers, 1979, 351 pp, $23.75.

*The 1979 Year Book of Anesthe-*

*siology* brings together pertinent abstracts published in the anesthesia and nonanesthesia literature up to November 1978. The format is similar to that used in past years with 23 categories ranging from basic pharmacology and physiology to subspecialty areas, intensive care, and pain treatment. The editors' comments, which follow many of the abstracts, reemphasize certain points and also raise interesting questions. Included is the current literature quiz with 62 questions cross-referenced to the abstracts.

The quality of this book depends almost entirely on the quality of the articles that are included. Thousands of articles were screened and this year 241 articles were personally selected by the editors. *The Year Book* is an excellent review of the medical literature which is pertinent to anesthesia.

Glenn A. Fromme, MD
Instructor
Mayo Medical School
Rochester, MN

## BOOKS RECEIVED

**Renal Function in Anaesthesia and Surgery,** by D. R. Bevan, London, Academic Press, 1979, 239 pp, $35.00.

**Pain—Association for Research in Nervous and Mental Disease, Volume 58,** edited by J. J. Bonica. New York, Raven Press, 1979, 420 pp, $35.00.

**International Anesthesiology Clinics, Volume 17,** edited by B. A. Britt. Boston, Little, Brown and Co, 182 pp, $35.00.

**Anaesthesia for Children,** by T.C.K. Brown and G. C. Fisk, Oxford, Blackwell Scientific Publications, 1979, 439 pp, $77.50.

**Anesthesia and Neurosurgery,** by J. E. Cottrell and H. Turndorf, St. Louis, C. V. Mosby Co, 1979, 433 pp, $47.50.

**Blood Gases and Acid-Base Physiology,** by N. L. Jones. New York, Brian C. Decker, 1980, 175 pp.

**Anesthesia for Obstetrics,** by S. M. Shnider and G. Levinson. Baltimore, Williams & Wilkins, 1979, 456 pp, $35.00.

# A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

## Editorial Policies

Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

**Types of materials.** The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

**Peer review.** All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

**Legal and ethical considerations.** Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

**Editing.** All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

## Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

**Title Page.** The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

**Abstract and Key Words.** The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Define all abbreviations except those approved by the International System of Units.

*Key (indexing) terms.* Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract.

**Text.** The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

*Introduction.* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods.* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

*Results.* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

*Discussion.* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**References.** (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus.* Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus.* Consult the "List of Journals Indexed," printed annually in the January issue of *Index Medicus.*

Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

*Journal*

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

*Books and Other Monographs*

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

**Tables.** Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

**Illustrations.** Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of *original* drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 12.7 by 17.3 cm (5 by 7 in) but no larger than 20.3 by 25.4 cm (8 by 10 in). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them using paper clips. Do not bend figures.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with background.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, *regardless of authorship or publisher,* except for documents in the public domain.

For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Some journals publish illustrations in color only if the author pays for the extra cost.

**Legends for Illustrations.** Type legends for illustrations double spaced, starting on a separate page with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

**Abbreviations.** Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

# Announcing a new pharmaceutical company that has already created over forty original drugs

# Janssen Pharmaceutica

**JANSSEN PHARMACEUTICA INC.**
501 George Street, New Brunswick, N.J. 08903

## Introducing a new company with 50 years of experience

Janssen Pharmaceutica, a new pharmaceutical company, draws on almost 50 years of experience in drug development and manufacturing. Part of the Johnson & Johnson family, Janssen is located in New Brunswick, New Jersey. Its parent company, headquartered in Beerse, Belgium, has long been recognized as one of the world's most innovative pharmaceutical firms.

The Janssen Research Centre, the key to Janssen's success, was established in 1953 by Dr. Paul Janssen. In just over 25 years, the Janssen Research Centre has made available to the medical profession over 40 original drugs. Most are available worldwide; many are now in wide use by physicians in the United States.

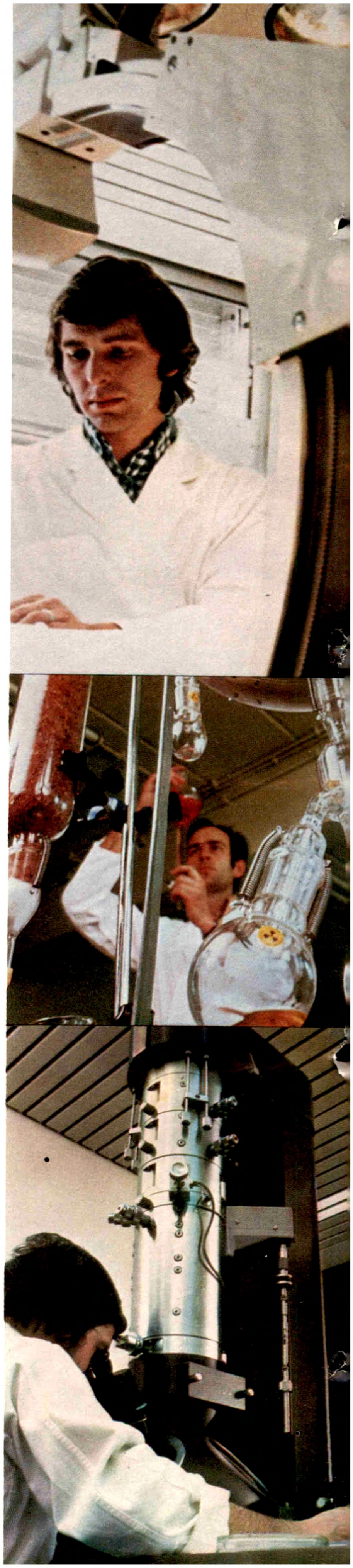
## Research at Janssen: a record of achievement, a promise of breakthroughs to come

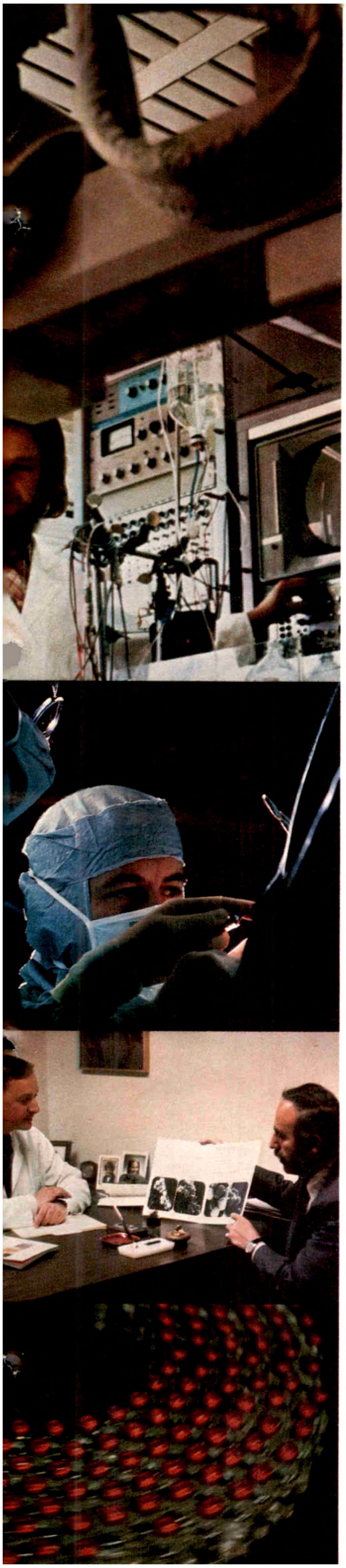
Janssen research has already produced a number of valuable drugs in areas important to modern medical practice. Included are compounds used in the treatment of mental disorders, infectious and cardiovascular diseases, immunologic dysfunctions, gastrointestinal and parasitological problems as well as several agents used in anesthesiology.

Janssen has opened new frontiers in the clinical application of a novel class of therapeutic agents: synthetic immunosupportive agents. Compounds exhibiting this type of activity have already proved valuable in treating a variety of disorders where a specific immunologic defect is involved and have helped add substantially to knowledge of the mechanism of the disease process.

Through the use of advanced techniques such as X-ray crystallography, nuclear magnetic resonance, the application of quantum mechanical principles and large digital computers, Janssen research is learning more each day about drug/receptor mapping and rational drug design. This knowledge has been—and will be—used to design new and better compounds: drugs which are more potent and more specific, drugs with greater therapeutic ratios, drugs which are simpler for the physician to use and easier for the patient to take.

Some products of Janssen's research efforts, already available in certain geographical areas, include: an analgesic molecule with a therapeutic ratio (lethal dose: effective dose) of 15,000:1, as compared to 250:1 for morphine, and a neuroleptic effective for a week or more after just one oral administration. Other areas where investigations have yielded promising compounds include cardiovascular, gastrointestinal and allergic diseases.





## To better serve the medical and allied professions

Janssen Pharmaceutica was founded in the United States to facilitate the introduction of original developments of Janssen research to the medical profession. Until now, Janssen products were available here only through other pharmaceutical companies. Some of these firms will continue to provide you with drugs they are now supplying, but we will make all new products available to you. Thus, there will be more direct communication between Janssen, the source, and you, the eventual user of Janssen products.

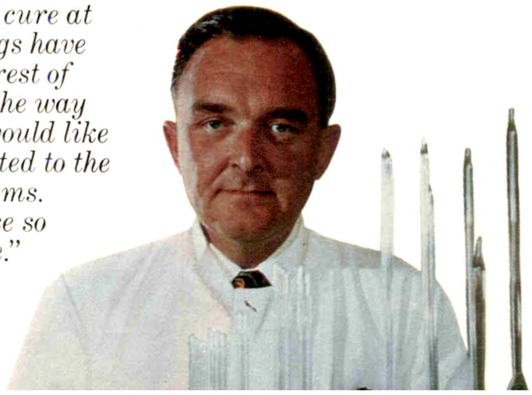
Contact with the health profession will be in the hands of a highly skilled corps of Janssen Pharmaceutica representatives who will be calling on teaching centers and hospitals as well as physicians' offices. Janssen representatives undergo thorough training, instruction which emphasizes not only product knowledge, but an understanding of the clinical situations where Janssen drugs are used. Representatives' skills are updated through educational programs which keep them apprised of the latest medical information as it pertains to the use of Janssen products. Thus, our representatives will be especially well equipped to provide you with the information you require.

Moreover, since their background and training will enable them to discuss your needs with you, our research and development can be guided by a knowledge of the direction of your practice. Another gain: our location in the United States will enable us to expedite the introduction of new products through the use of clinical research and development facilities available to us here.

## The Janssen commitment

Every company has a guiding principle which forms the basis of its activities and directs its major efforts. With Janssen, this principle is a commitment to research. The nature and depth of our dedication have best been expressed by Dr. Paul Janssen, President and Director of Research of the parent company.

*"There are still many severe problems for which there is no cure at all and for which effective drugs have to be found quickly in the interest of all who are suffering. This is the way we see our duty here and we would like to think that we have contributed to the solution of some of these problems. And we will continue...because so much more remains to be done."*



Janssen Pharmaceutica, 2340 Beerse, Belgium

## Janssen Pharmaceutica today... and tomorrow

At this time, Janssen Pharmaceutica is making five proven drugs available to the medical profession. Produced in facilities which make use of the most modern and sophisticated manufacturing and packaging equipment, these are:

SUBLIMAZE® (fentanyl) injection ©
INAPSINE® (droperidol) injection
INNOVAR® (droperidol/fentanyl) injection ©
MONISTAT i.v.™ (miconazole for intravenous infusion)
VERMOX® (mebendazole) Tablets

While other Johnson and Johnson firms have previously made these products available in the United States, they will now be supplied exclusively by Janssen Pharmaceutica. In the sense that they represent important therapeutic advances in their specific areas of usefulness, they are typical of the Janssen research achievement.

We expect to introduce one important new therapeutic agent to the medical profession sometime in the course of 1980, and more will follow as current projects come to fruition. With the present drugs and with those that we hope to make available in time, we confidently expect that Janssen Pharmaceutica will make itself felt as an important force in the American pharmaceutical industry in the years to come.

**Committed to research...**
**because so much remains to be done.**

**JANSSEN PHARMACEUTICA INC.**
501 George Street, New Brunswick, N.J. 08903

JP-006 Printed in U.S

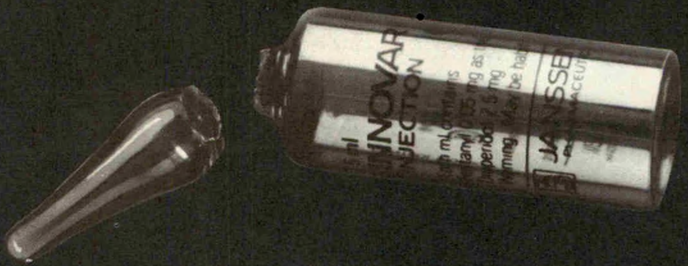
Now from
Janssen Pharmaceutica:

anesthetic adjuncts
proven by over
a decade of worldwide
experience

Charting the course of
balanced anesthesia

JANSSEN PHARMACEUTICA INC.
501 George Street, New Brunswick, N.J. 08903

# As an aid to induction, Innovar® INJECTION Ⓒ (droperidol/fentanyl) can help

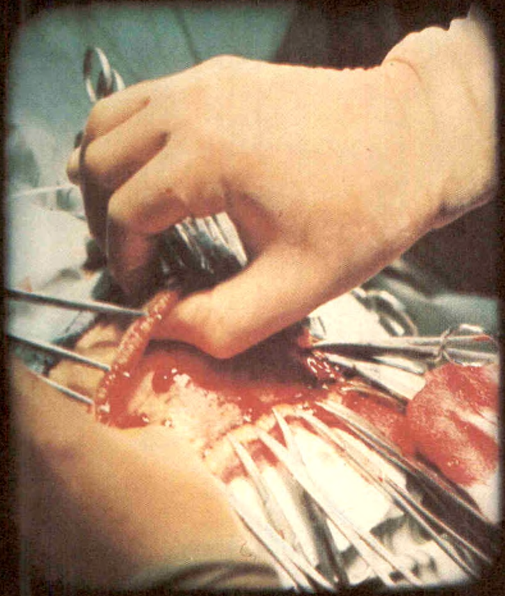


**Committed to research…**
**because so much remains to be done**

**JANSSEN PHARMACEUTICA INC**
501 George Street, New Brunswick, N.J. 089

## 1. Establish a foundation of tranquility and analgesia

Smooth intubation
Minimize the need for thiopental



## 2. Foster a smooth and uneventful intraoperative course

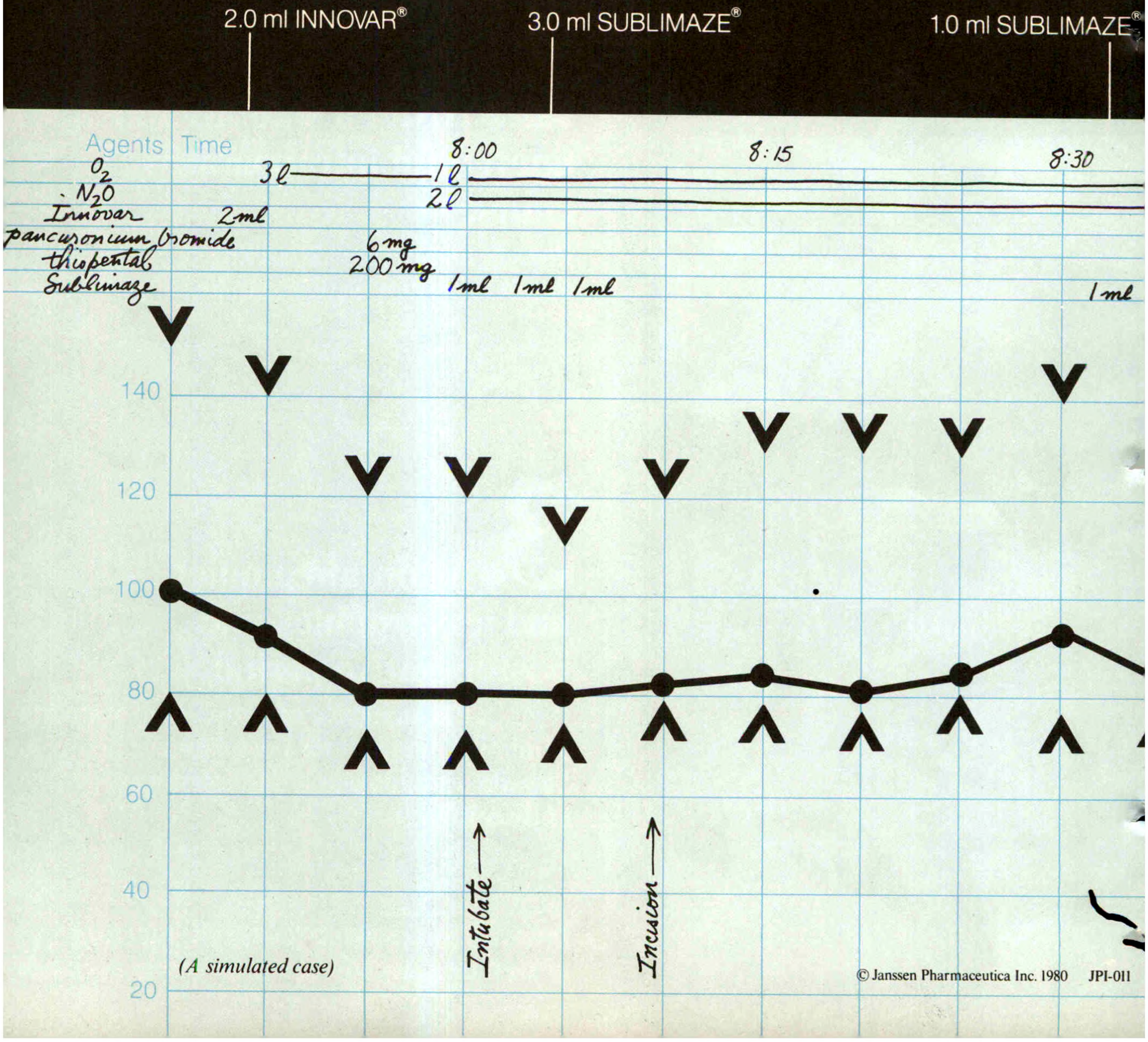
Provide an anesthetic baseline
Promote cardiovascular stability

## 3. Maintain a quiet and less troublesome postoperative period

Reduce the incidence of nausea and vomiting
Minimize the need for postoperative analgesic
Provide tranquilization and tolerance of discomfort

**Innovar® (droperidol/fentanyl) injection Ⓒ**
**proven by a decade of worldwide experience**

# Adequate analgesia with Sublimaze® INJECTION Ⓒ (fentanyl) can help suppress surgical stress



(A simulated case)

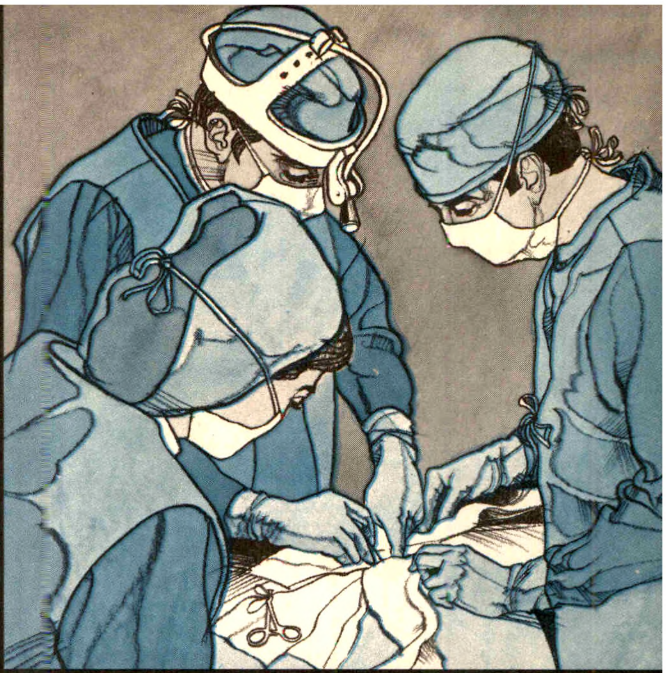
© Janssen Pharmaceutica Inc. 1980 JPI-011

**Administered following induction, 3-5 ml of SUBLIMAZE® (fentanyl) injection Ⓒ will:**

- provide profound analgesia
- minimize catecholamine release
- lay a foundation for a smooth intraoperative course

**Used as needed during surgery, SUBLIMAZE® offers controllable analgesia:**

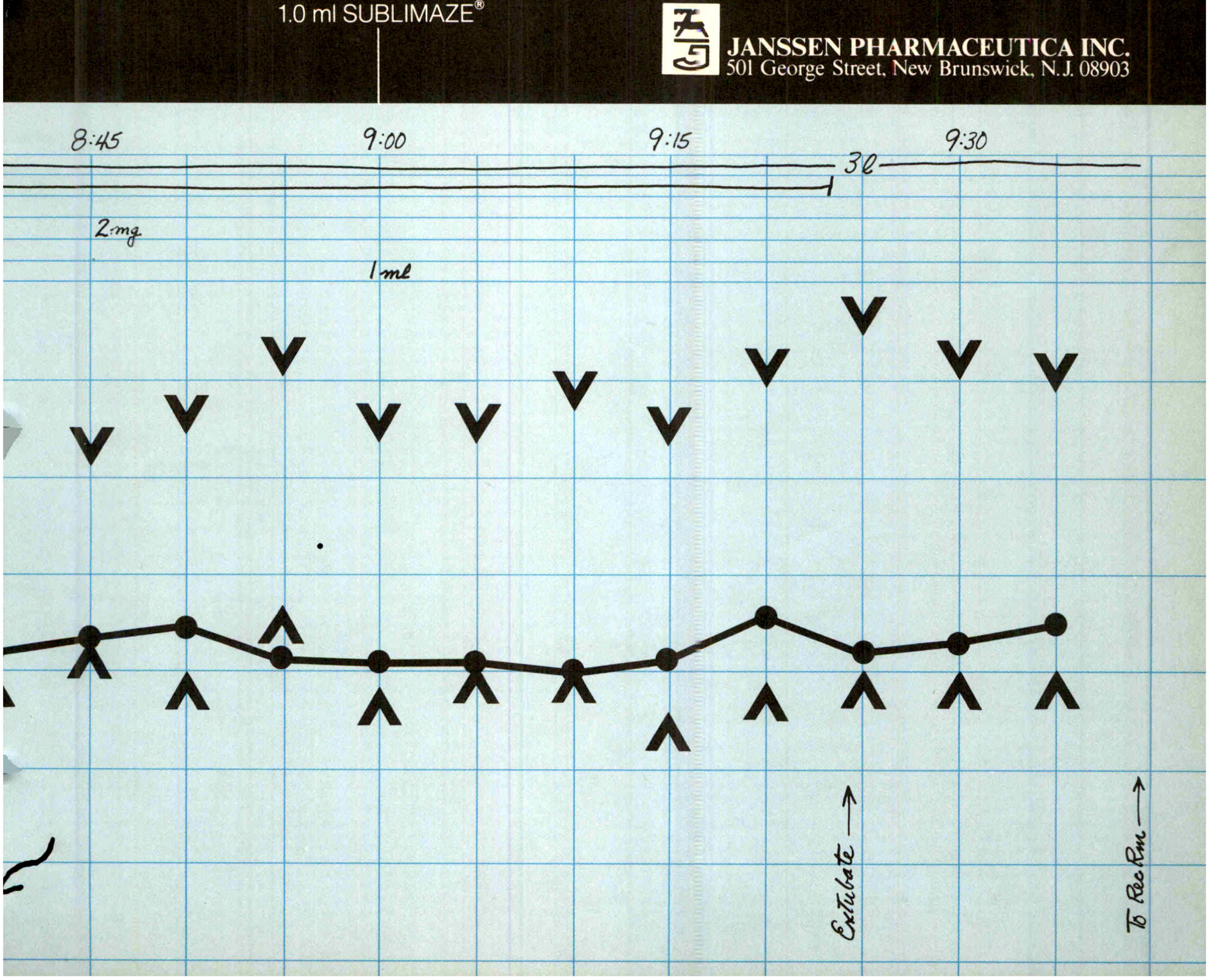
- rapid onset
- short duration of action*
- rapid reversibility by narcotic antagonists*
- analgesic action carries over into postoperative period*



*The respiratory depressant effect of Sublimaze® (fentanyl) injection Ⓒ may last longer than the analgesic effect.

*Please see Prescribing Information on following pages*

**JANSSEN PHARMACEUTICA INC.**
501 George Street, New Brunswick, N.J. 08903



# **Innovar**® Injection CII ℞

## FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

The two components of INNOVAR injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

**DESCRIPTION:** Each ml. contains (in a 1:50 ratio):

| | |
|---|---|
| Fentanyl | 0.05 mg. |
| as the citrate | |
| *Warning:* May be habit forming | |
| Droperidol | 2.5 mg. |

Lactic acid for adjustment of pH to 3.5 ± 0.3

**ACTIONS:** INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 ml.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single I.V. dose of up to 0.1 mg. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

As with longer-acting narcotic analgesics, the duration of the respiratory depressant effect of *SUBLIMAZE* (fentanyl) may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to $CO_2$ stimulation following administration of fentanyl to man:

1. DIMINISHED SENSITIVITY TO $CO_2$ STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE. Fentanyl frequently slows the respiratory rate but this effect is seldom noted for over 30 minutes regardless of the dose administered.
2. Duration and degree of respiratory depression is dose related.
3. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.
4. Altered sensitivity to $CO_2$ stimulation has been demonstrated for up to four hours following a single intravenous dose of 0.6 mg. (12 ml.) fentanyl to healthy volunteers.

See also WARNINGS and PRECAUTIONS concerning respiratory depression.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha-adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of fentanyl.

**INDICATIONS:** INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, *SUBLIMAZE*® (fentanyl) injection alone rather than the combination drug INNOVAR injection, should usually be used; see Dosage and Administration Section.

**CONTRAINDICATIONS:** INNOVAR injection is contraindicated in patients with known intolerance to either component.

**WARNINGS:** AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in PRECAUTIONS and OVERDOSAGE.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

*The respiratory depressant effect of narcotics persists longer than the measured analgesic effect. When used with* INNOVAR *injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended.*

INNOVAR injection *may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.*

***Drug Dependence:*** *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of INNOVAR injection or *SUBLIMAZE* (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

***Head Injuries and Increased Intracranial Pressure:*** INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, INNOVAR injection may obscure the clinical course of patients with head injury.

***Usage in Children:*** The safety of INNOVAR injection in children younger than two years of age has not been established.

***Usage in Pregnancy:*** The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

**PRECAUTIONS:** *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilation and hypotension because of sympathetic blockade. Through other mechanisms (see Actions), fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in the moving and positioning of patients because of a possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and *SUBLIMAZE* (fentanyl), should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperative respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl (as *SUBLIMAZE* (fentanyl) or INNOVAR) employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection, the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

**ADVERSE REACTIONS:** The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INNOVAR injection. Restlessness, hyperactivity and anxiety which can be either the result of inadequate tranquilization or part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-Parkinson agents.

Elevated blood pressure, with and without preexisting hypertension, has been reported following administration of INNOVAR injection. This might be due to unexplained alterations of sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, laryngospasm, bronchospasm, bradycardia, tachycardia, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

**DOSAGE AND ADMINISTRATION:** *Dosage should be individualized.* Some of the factors to be considered in determining dose are age, body weight, physical status, underlying pathological condition, use of other drugs, the type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Most patients who have received INNOVAR injection do not require narcotic analgesics during the immediate postoperative period. It is recommended that narcotic analgesics, when required, be used initially in reduced doses, as low as ¼ to ⅓ those usually recommended.

***Usual Adult Dosage:***

I. *Premedication*—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—0.5 to 2.0 ml. may be administered *intramuscularly* 45 to 60 minutes prior to surgery with or without atropine.

II. *Adjunct to General Anesthesia–Induction*—1 ml. per 20 to 25 pounds of body weight may be administered slowly intravenously. Smaller doses may be adequate.

The total amount of INNOVAR injection administered should be carefully titrated to obtain the desired effect based on the individual patient's response.

There are several methods of administration of INNOVAR injection for induction of anesthesia.

A. Intravenous injection—To allow for the variable needs of patients INNOVAR injection may be administered intravenously in fractional parts of the calculated dose. With the onset of somnolence, the general anesthetic may be administered.

B. Intravenous drip—10 ml. of INNOVAR injection are added to 250 ml. of 5% dextrose in water and the drip given rapidly until the onset of somnolence. At that time, the drip may be either slowed or stopped and the general anesthetic administered.

*Maintenance*—INNOVAR injection is not indicated as the sole agent for the maintenance of surgical anesthesia. It is customarily used in combination with other measures such as nitrous oxide-oxygen, other inhalation anesthetics, and/or topical or regional anesthesia.

To prevent the possibility of excessive accumulation of the relatively long-acting droperidol component, *SUBLIMAZE* (fentanyl) alone should be used in increments of 0.025 to 0.05 mg. (0.5 to 1.0 ml.) for the maintenance of analgesia in patients initially given INNOVAR injection as an adjunct to general anesthesia. (See *SUBLIMAZE* (fentanyl) package insert for additional prescribing information.) However, in prolonged operations, additional 0.5 to 1.0 ml. amounts of INNOVAR injection may be administered with caution intravenously if changes in the patient's condition indicate lightening of tranquilization and analgesia.

III. *Use Without a General Anesthetic in Diagnostic Procedures*—Administer the usual I.M. premedication (0.5 to 2.0 ml.) 45 to 60 minutes before the procedure. To prevent the possibility of excessive accumulation of the relatively long-acting droperidol component, *SUBLIMAZE* (fentanyl) alone should be used in increments of 0.025 to 0.05 mg. (0.5 to 1.0 ml.) for the maintenance of analgesia in patients initially given INNOVAR injection. (See *SUBLIMAZE* (fentanyl) package insert for additional information). However, in prolonged operations, additional 0.5 to 1.0 ml. amounts of INNOVAR injection may be administered with caution intravenously if changes in the patient's condition indicate lightening of tranquilization and analgesia.

Note: When INNOVAR injection is used in certain procedures such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. *Adjunct to Regional Anesthesia*—1 to 2 ml. may be administered intramuscularly or slowly intravenously when additional sedation and analgesia are required.

***Usual Children's Dosage:***

I. *Premedication*—0.25 ml. per 20 lbs. body weight administered *intramuscularly* 45 to 60 minutes prior to surgery with or without atropine.

II. *Adjunct to General Anesthesia*—The total combined dose for induction and maintenance averages 0.5 ml. per 20 lbs. body weight. Following induction with INNOVAR injection, *SUBLIMAZE* (fentanyl) alone in a dose of ¼ to ⅓ that recommended in the adult dosage section should usually be used when indicated to avoid the possibility of excessive accumulation of droperidol. However, in prolonged operations, additional increments of INNOVAR injection may be administered with caution when changes in the patient's condition indicate lightening of tranquilization and analgesia.

See Warnings and Precautions for use of INNOVAR injection with other CNS depressants, and in patients with altered response.

**OVERDOSAGE:** ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

***Treatment:*** In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate counter-measures. The duration of respiratory depression following overdose of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package inserts of the individual narcotic antagonists for details about use.

**HOW SUPPLIED:** INNOVAR® injection is supplied in 2 ml. and 5 ml. ampuls, in packages of 10.

U.S. Patent No. 3,141,823 Rev. 1/80

# **Sublimaze®** (fentanyl) injection Ⓒ ℞

**DESCRIPTION:** Each ml. contains:
Fentanyl .......... 0.05 mg.
as the citrate

*Warning:* May be habit forming.

Sodium hydroxide for adjustment of pH to 4.0-7.5.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

**ACTIONS:** SUBLIMAZE (fentanyl) is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE (fentanyl) in a dose of 0.1 mg. (2.0 ml.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE (fentanyl) appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as in *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE (fentanyl).

SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE (fentanyl) is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single I.V. dose of up to 0.1 mg. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is one to two hours. As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of SUBLIMAZE (fentanyl) may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to $CO_2$ stimulation following administration of fentanyl to man:

1. DIMINISHED SENSITIVITY TO $CO_2$ STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE. Fentanyl frequently slows the respiratory rate, but this effect is seldom noted for over 30 minutes regardless of the dose administered.
2. Duration and degree of respiratory depression is dose related.
3. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.
4. Altered sensitivity to $CO_2$ stimulation has been demonstrated for up to four hours following a single intravenous dose of 0.6 mg. (12 ml.) fentanyl to healthy volunteers.

See also WARNINGS and PRECAUTIONS concerning respiratory depression.

**INDICATIONS:** SUBLIMAZE (fentanyl) is indicated:
—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate post-operative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as *INAPSINE®* (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

**CONTRAINDICATIONS:** SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

**WARNINGS:** AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (FENTANYL) SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available*.

*As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended.* SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

***Drug Dependence:*** SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

***Head Injuries and Increased Intracranial Pressure:*** SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

***Usage in Children:*** The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

***Usage in Pregnancy:*** The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

**PRECAUTIONS:** *The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol), hypotension can occur. If this occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol). When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

**ADVERSE REACTIONS:** As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without preexisting hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with INAPSINE (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** *Dosage should be individualized.* Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

***Usual Adult Dosage:***

I. *Premedication* (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—0.05 to 0.1 mg. (1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia Induction*—0.05 to 0.1 mg. (1 to 2 ml.) may be administered initially intravenously and may be repeated at 2 to 3 minute intervals until desired effect is achieved. A reduced dose as low as 0.025 to 0.05 mg. (0.5 to 1 ml.) is recommended in elderly and poor-risk patients.

*Maintenance*—0.025 to 0.05 mg. (0.5 to 1 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

If *INNOVAR®* injection is administered in addition to SUBLIMAZE (fentanyl), the calculation of the recommended dose of SUBLIMAZE (fentanyl) should include the fentanyl contained in the *INNOVAR* injection. See *INNOVAR* injection Package Insert for full prescribing information.

III. *Adjunct to Regional Anesthesia*—0.05 to 0.1 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional analgesia is required.

IV. *Postoperatively (recovery room)*—0.05 to 0.1 mg. (1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

***Usual Children's Dosage:*** For induction and maintenance in children two to 12 years of age, a reduced dose as low as 0.02 to 0.03 mg. (0.4 to 0.6 ml.) per 20 to 25 pounds is recommended. See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

**OVERDOSAGE:** ***Manifestations:*** The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

***Treatment:*** In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

**HOW SUPPLIED:** 2 ml. and 5 ml. ampuls—packages of 10.

U.S. Patent No. 3,164,600 Rev. 1/80

## Committed to research...
## because so much remains to be done.

JANSSEN PHARMACEUTICA INC., New Brunswick, New Jersey 08903

# *Anesthesia and Analgesia*

## BACK ISSUES AVAILABLE

### Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | 4 | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | 4 | 5 | 6 |
| 36 | 1957 | – | 2 | – | – | – | 6 | 44 | 1965 | – | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | 3 | 4 | 5 | 6 |
| 38 | 1959 | – | 2 | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | 5 | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | 2 | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | 3 | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | 4 | 5 | – |

### Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | 2 | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | 3 | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

### Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 |
| 59 | 1980 | 1 | | | | | |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.
BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955
OTHER PUBLICATIONS AVAILABLE:

- "Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.
- Ten-Year (1960-1969) Cumulative Index—$3.00.
- Ten-Year (1970-1979) Cumulative Index—$3.00.
- 1979 (53rd Congress) Review Course Lectures—$3.00.
- 1980 (54th Congress) Review Course Lectures & Abstracts—$3.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $______ enclosed.
☐ Please send bill with understanding that ordered material will be sent when payment is received. •

Name ______________________________
Address ______________________________
City, State, Zip ______________________________

*International Anesthesia Research Society*

Publisher of ANESTHESIA and ANALGESIA

3645 Warrensville Center Road, Cleveland, Ohio 44122, U.S.A.

## I.A.R.S. EDUCATIONAL MEMBERSHIP

**SPONSORING ORGANIZATION:** The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio. It serves the Specialty in two ways: (1) By publication of a bi-monthly journal entitled "Anesthesia and Analgesia"; and (2) By sponsorship of an annual scientific ("Congress") meeting in March of each year. The I.A.R.S. is independent of, and has no affiliation or membership-exchange arrangement with any other anesthesia society or association:

**PURPOSE OF EDUCATIONAL MEMBERSHIP:** To financially assist students in anesthesiology or anesthesia-related training programs by making available to them, during the effective term of their Educational Membership:

(1) A one-half price subscription to "Anesthesia and Analgesia" and
(2) Complimentary registration at the annual scientific meeting.

**WHO IS ELIGIBLE FOR EDUCATIONAL MEMBERSHIP:**

I Residents and Fellows (Interns) enrolled in training programs in the medical, osteopathic or dental professions;

II Nurses with a diploma or degree in nursing who are enrolled in nurse anesthesia schools;

III Students enrolled in programs leading to certification as Physician Assistants in Anesthesia/Anesthesiologist Assistants/Physician Associates in Anesthesiology; and

Students enrolled in programs leading to certification as Respiratory Therapists or Technicians.

**MEMBERSHIP TERMS AND COSTS:** There are two membership periods available. The applicable membership dues must be paid in full with the application (i.e., annual payments of $15 will not be accepted.)

**Two-Year Term—$30.00:** Individuals applying for this period should have at least 18 months remaining in their training program at the time of application:

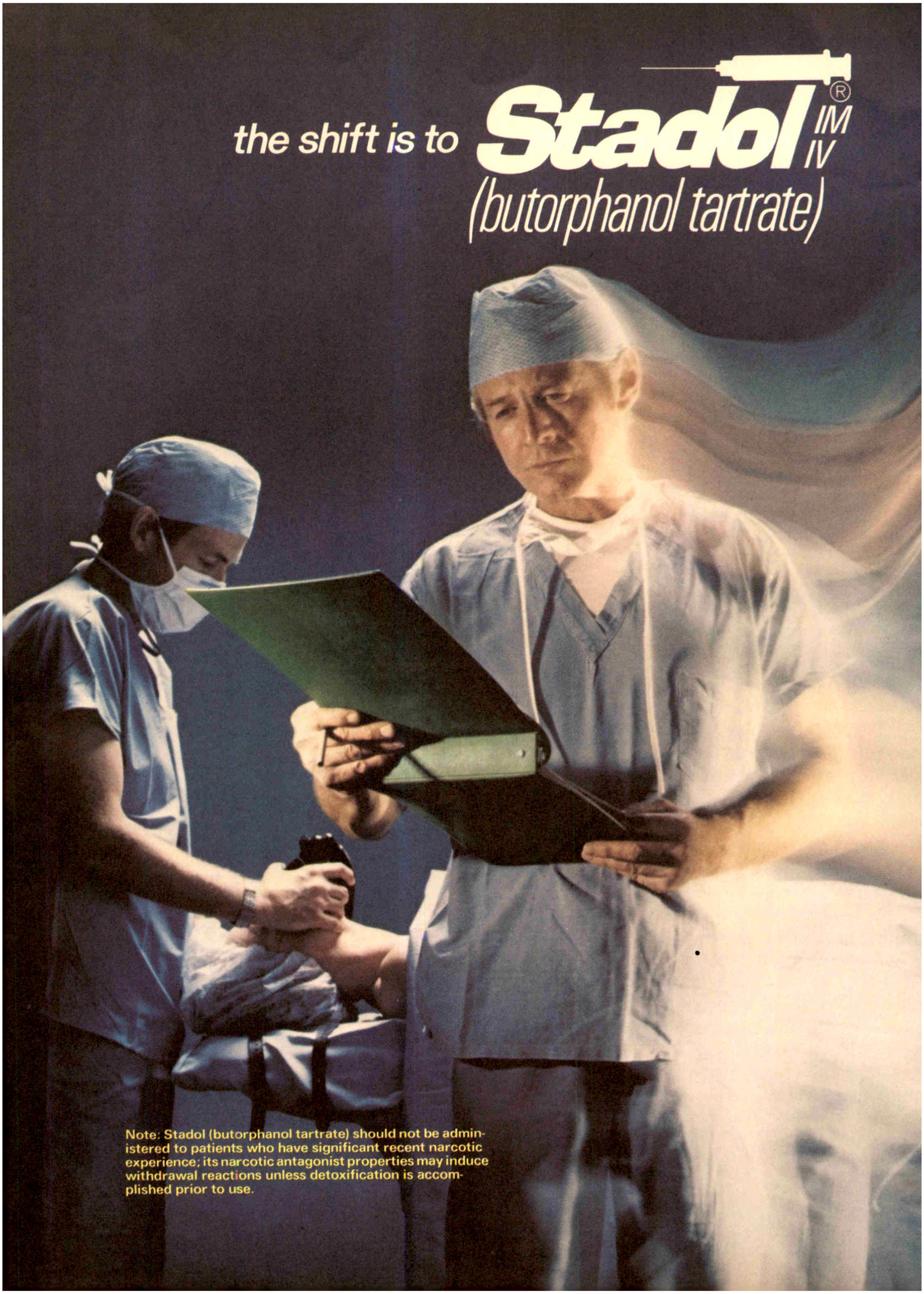
**Three-Year Term—$45.00:** Individuals applying for this period should have at least 30 months remaining in their training program at the time of application.

**Note:** The Educational Membership term should not extend more than six months following the ending of the training program covered. To that end, I.A.R.S. may, at its option, enter memberships retroactively to conform. In such instances, back issues of the Journal will be sent so that all 2-year memberships include 12 Journals, and all 3-year memberships include 18 Journals.

**CANCELLATION OF MEMBERSHIP:** Educational Membership can be cancelled upon written request to the IARS, and return of membership card, if the member is no longer enrolled in the training program. Pro-rated refunds will be made at the discretion of the I.A.R.S.

**CONTINUATION OF MEMBERSHIP:** After completion of the Educational Membership period, and upon payment of membership dues then in effect, individuals in Category I will be automatically continued as Members; and individuals in Categories II and III will be automatically continued as Associate Members of the I.A.R.S.

**APPLICATION FORMS:** The official application form (or facsimile thereof) must be used in applying for this membership, and payment must be submitted with the application. Application forms are available from the Cleveland business office, address above.


the shift is to Stadol® IM IV
(butorphanol tartrate)

Note: Stadol (butorphanol tartrate) should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.

*for pain management*

**preoperatively**
**intraoperatively**
**postoperatively**

*in surgery*

- **proven analgesic efficacy**—as a pre- and postoperative agent . . . for patients in labor . . . as the analgesic component of balanced anesthesia
- **fast acting**—onset of action within 10 minutes IM, very rapidly IV; peak analgesic activity within 30-60 minutes IM, more rapidly IV
- **limited respiratory depressant potential**—2 mg of Stadol produces a degree of respiratory depression similar to that of 10 mg of morphine or 70 mg of meperidine—unlike these agents, doubling the Stadol dose to 4 mg does not appreciably increase the magnitude of respiratory depression
- **favorable side effect profile**—low physical dependence liability, little nausea or vomiting, infrequent constipation
- **few CNS effects other than sedation**—the reported incidence of euphoria and hallucinations is less than 1%
- **nonscheduled**—not subject to regulations under the Federal Controlled Substances Act

**Stadol® IM IV**
(butorphanol tartrate)

*proven performance in the relief of moderate to severe pain*

**BRISTOL™**

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

Please see brief summary of prescribing information on the following page.

Copyright ©1980, Bristol Laboratories

**Brief Summary of Prescribing Information**
**STADOL® (butorphanol tartrate)**

For complete information, consult Official Package Circular.

(2) 12/10/79

**INDICATIONS AND USAGE**—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

**CONTRAINDICATIONS**—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

**WARNINGS—Patients Physically Dependent on Narcotics:** Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

**Drug Dependence:** Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

**Head Injury and Increased Intracranial Pressure:** Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

**Cardiovascular Effects:** Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

**PRECAUTIONS—Certain Respiratory Conditions:** Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

**Impaired Renal or Hepatic Function:** Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

**Biliary Surgery:** Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

**Usage as a Preoperative or Preanesthetic Medication:** Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

**Usage in Balanced Anesthesia:** The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

**Usage in Pregnancy:** The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

**Usage in Labor and Delivery:** Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

**Usage in Nursing Mothers:** The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

**Usage in Children:** Safety and efficacy in children below age 18 years have not been established.

**ADVERSE REACTIONS**—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

**CNS:** nervousness, unusual dreams, agitation, euphoria, hallucinations

**Autonomic:** flushing and warmth, dry mouth, sensitivity to cold

**Cardiovascular:** palpitation, increase or decrease of blood pressure

**Gastrointestinal:** vomiting

**Respiratory:** slowing of respiration, shallow breathing

**Dermatological:** rash or hives

**Eye:** diplopia or blurred vision

**OVERDOSAGE—Manifestations:** Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

**Treatment:** The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

**HOW SUPPLIED**—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

**NDC** 0015-5644-20—2 mg per ml, 2-ml vial
**NDC** 0015-5645-20—1 mg per ml, 1-ml vial
**NDC** 0015-5646-20—2 mg per ml, 1-ml vial
**NDC** 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
**NDC** 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

**BRISTOL™**

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

# ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA, effective

**From**—(Current or former address)

Street Address

City, State, Zip Code

**Important: Show your name and address exactly as your Journal is now addressed.**

**To**—(New Address)

Street Address

City, State, Zip Code

Print Your Name

## Cook County Graduate School of Medicine

announces

### SPECIALTY REVIEW COURSE IN ANESTHESIOLOGY

**May 11–16, 1980**

Alon P. Winnie, M.D., *Course Coordinator*
Chairman, Department of Anesthesia
Abraham Lincoln School of Medicine
University of Illinois

A six-day intensive review course which examines, in-depth, the clinical practice of Anesthesiology and the fundamental principles upon which it is based.

*A.M.A. Category I Credit: 54 Hours*

For further information and registration contact:

**Cook County Graduate School of Medicine**
**707 South Wood Street, Chicago, Illinois 60612**
**(312) 733-2800**

### *I.A.R.S. 1979*
### *REVIEW COURSES*

Booklet containing 14 Review Course Lectures given at 53rd Congress in March of 1979 is available from I.A.R.S. Cleveland business office at $5.00 per copy. Supply is limited and orders will be filled on basis of receipt date of order. Make checks payable to International Anesthesia Research Society and send with order.

STATE UNIVERSITY of NEW YORK

Upstate Medical Center

### STAFF ANESTHESIOLOGIST

Two positions at the rank of Assistant or Associate Professor will be available after January 1, 1980. Responsibilities include teaching, at the undergraduate, graduate and postgraduate levels, research and service. Four years of postgraduate training and eligibility for a New York license is required. An interest in regional anesthesia, pain therapy or intensive care advantageous, but not essential. Highly competitive salary structure and excellent fringe benefits.

*Send curriculum vitae to:*

Howard L. Zauder, M.D., Ph.D.
Professor and Chairman
Department of Anesthesiology
State University of New York
Upstate Medical Center
Syracuse, New York 13210

# classified ADVERTISING

### PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles has advanced clinical program for residents at the second and third year level of training. Also accepting applications from practicing anesthesiologists who wish to update their knowledge and proficiency. Positions available from 2 months to 1 year. Specialized year approved by the AMA. For further details contact:

George B. Lewis, Jr., MD
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, CA 90027
Phone (213) 662-1708

### MARYLAND:

The Maryland Institute for Emergency Medical Services Systems is seeking staff anesthesiologists with an interest and/or experience in critical care, trauma anesthesia and/or neuro-surgical anesthesia/critical care. MIEMSS is the 85 bed clinical center for trauma care and research in the State of Maryland. Teaching and research opportunities in a multidisciplinary setting are available. Salary negotiable, liberal fringe benefits. Send curriculum vitae to: Peter Chodoff, M.D., M.P.H., Chief, Critical Care/Anesthesia, Maryland Institute for Emergency Medical Services Systems, Baltimore, Maryland 21201

### MAYO FOUNDATION, DEPARTMENT OF ANESTHESIOLOGY—

Opportunities for advanced subspecialty training in cardiovascular and neuro-anesthesia, respiratory intensive care, and pain management are available to qualified candidates. Indepth training experience in one or more of these areas for periods of six months to two years may be arranged. For additional details, contact: Alan D. Sessler, M.D., Chairman, Department of Anesthesiology, Mayo Foundation, Rochester, Minnesota 55901.

### ANESTHESIOLOGIST

Position available for an Anesthesiologist in an active 460-bed general medical and surgical teaching hospital with strong affiliation with University of Missouri Medical School. Prefer candidate who is board certified or eligible. Licensure in any of the 50 states acceptable. Salary range $40,000 to $50,112 per year dependent on qualifications plus handsome bonus. Liberal fringe benefits. Call or write Warren P. Sights, M.D., Acting Chief of Staff, Harry S. Truman Memorial Veterans Hospital, 800 Stadium Road, Columbia, MO 65201, phone (314) 443-2511 ext. 6010. An Equal Opportunity Employer.

### ANESTHESIOLOGISTS:

90 member multispecialty group adjacent to modern accredited 500 bed hospital seeks Board eligible or certified specialist to join associates; located in upper midwest university metropolitan area of 110,000; thirty-five minutes from superb clean lake region; associated with four year medical school; outstanding income; all specialties represented; will pay travel expenses for physician and spouse for interview. Write Box 3-80-A, ℅ I.A.R.S.

### ANESTHESIOLOGIST

Board certified or eligible to join M.D.'s and CRNA's in 380-bed hospital. Prefer recently trained in all techniques. Please send CV to Belleville Anesthesia Associates, P. O. Box 1232, Belleville, Illinois 62223.

### MISSOURI

Anesthesiologist wanted to join private group practice. 400-bed hospital with all specialties except open heart; little OB. Town of 100,000 with good schools, close airport, and good recreation. Excellent starting income, fringes, and potential. Reply to Box 7-79-A, c/o I.A.R.S.

### ANESTHESIOLOGIST

Needed in small Minnesota city. Challenging cases, no open heart. Malpractice insurance paid. Salary first year, then buy-in. Reply to Box 9-79-H, c/o I.A.R.S.

### MASSACHUSETTS

Anesthesiologist needed to join private group practice in 300-bed hospital in town of 20,000, servicing an area population of 70,000 in rural New England. All specialties except open heart. Good schools, recreation, transportation. Salary first year with fringes—then full partnership. Reply to Box 4-80-B, ℅ I.A.R.S.

### TULANE UNIVERSITY, New Orleans, Louisiana

Position available in July 1980 for a staff academic anesthesiologist. Responsibilities in clinical, teaching and research areas. Tulane University is an Affirmative Action/Equal Opportunity employer. Send Curriculum Vitae to: Robert R. Kirby, M.D., Department of Anesthesiology, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112.

### UNIVERSITY OF CALIFORNIA, IRVINE

The Department of Anesthesiology, University of California, Irvine, has faculty positions open at junior and senior levels. Rank will be commensurate with experience and qualifications. Positions are available in all fields, although special expertise in neurological anesthesia, cardiac anesthesia, intensive care and/or pain management is desirable. Candidates must have demonstrated skills in teaching, research, and patient care activities, be Board certified/eligible, and possess California State license. Women and minorities are encouraged to apply. Send curriculum vitae and names of three references to Bruce F. Cullen, M.D., University of California, Irvine, Department of Anesthesiology, Route 81A, 101 City Drive South, Orange, CA 92668.

# classified
# ADVERTISING

**ANESTHESIOLOGIST NEEDED**

Position available immediately for Board Certified or eligible anesthesiologist. P.A. includes physician anesthesiologists and CRNAs. All types of anesthesia are provided in 900 bed medical center, including open heart and neuro. Located in beautiful Sun Belt city. Reply to Box 4-80-A, ℅ I.A.R.S.

**ANESTHESIOLOGIST**

Excellent opportunity to begin private practice and direct the anesthesiology department of a 185 bed general hospital, with 2 C.R.N.A.'s. A rapidly expanding community 45 miles from excellent educational, professional contacts in St. Louis. Contact: J. T. Farrell, Executive Vice President, Administrator, St. Francis Mercy Hospital, 200 Madison Ave., Washington, MO 63090. Equal Opportunity Employer.

*Rates for classified advertising: $3.00 per line, minimum 5 lines; box number ads $3.50 per line. Classified display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia, 3645 Warrensville Center Rd., Cleveland, OH 44122.*

# INDEX OF ADVERTISERS

Ayerst Laboratories—*Fluothane®* (18), (19), (20)

Breon Laboratories Inc.—*Marcaine* (22), (23)

Bristol Laboratories—*Stadol* (40), (41), (42)

Classified Advertising (44), (45)

Cook County Graduate School of Medicine—*Specialty Review Course* (43)

Endo Laboratories—*Narcan®* (14), (15), (16)

Graphic Controls Corporation—*ECG Monitoring Electrode* Cover 4

Janssen Pharmaceutica, Inc.—*Institutional; Innovar; Sublimaze,* (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37)

K & G Healthcare Industries, Inc.—*Nicholes II Filter* (6), (7)

La Barge, Inc.—*Surgical Temperature Monitoring System* Cover 2

NASCO—*Spinal Injection Simulator* (17)

NDM Corporation—*NDM Electrodes* (11)

North American Drager—*Anesthesia Products* (24)

North American Drager—*Phillips Laryngoscope Blades* (17)

Parke-Davis—*Ketalar®* (4), (5)

Physio-Control Corporation—*Lifepak 6* Cover 3

Roche Laboratories—*Valium Injectable* (8), (9), (10)

Siemens/Elema AB—*Servo Humidifier* (12), (13)

State University of New York—*Employment Opportunity* (43)

## When you buy from Physio-Control, you get more than just a machine.

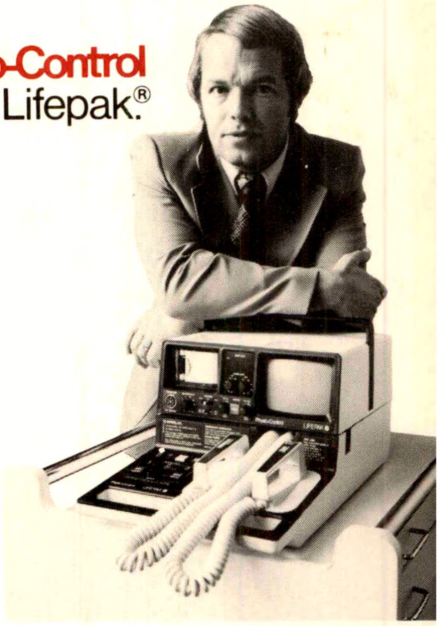
You get people. *Committed* people. You get the largest and most responsive service organization in the industry. The best trained. The most dedicated. Factory-direct and nationwide.

It's no accident either.

At Physio-Control, we pride ourselves on producing the most advanced acute cardiac care systems in the world. But excellence of product isn't enough. A life-saving system must have service to match.

You stand behind your work. So do we.

Only **Physio-Control**
makes the Lifepak.®



Physio-Control Corporation is the world leader in acute cardiac care systems. 11811 Willows Road, Redmond, Washington 98052
(206) 883-1181/Telex: 32-0166 Cable: PHYSIO/RED Lifepak and Physio-Control are registered trademarks.

# Jnround Is Better.

## The unround Offset and Offset Dx ECG monitoring electrode… ›specially created to solve problems.

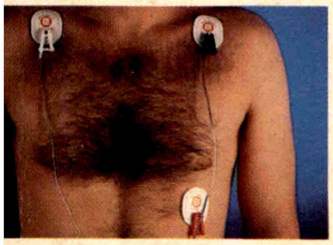
**Jnround for secure, ınrestricted electrode ›lacement.**
'he unique elliptical design ›f Offset electrodes permits ›lacement on almost any body ›ite and ensures conformation › body contours. The special ›eat activated adhesive resists ›ontact loss due to perspiration ›even when used on diaphoretic ›atients) and loosening action ›aused by prep solutions.

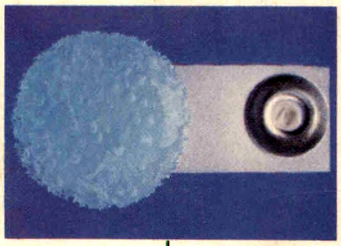
**Unround to reduce motion artifact and ensure base-line stability.**
The Medi-Trace® Offset electrode separates the snap from the gel column, connecting them with a silver/silver chloride conductor. The result? Little or no movement of the gel column, producing a superior trace that virtually eliminates motion artifact. Since the snap is over the adhesive, leadwire induced artifact and loose electrodes caused by leadwire tugging are virtually eliminated.

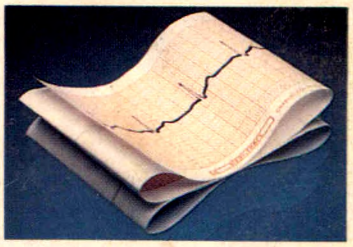
**Unround, the result of new technology in ECG monitoring electrodes.***
Advanced technology assures unprecedented conductivity and an end to trace deterioration problems. Specially formulated gel prevents premature dry-out and provides low impedance for a strong, reliable trace. In actual defibrillation tests, Offset electrode trace recovery occurred in less than one second!

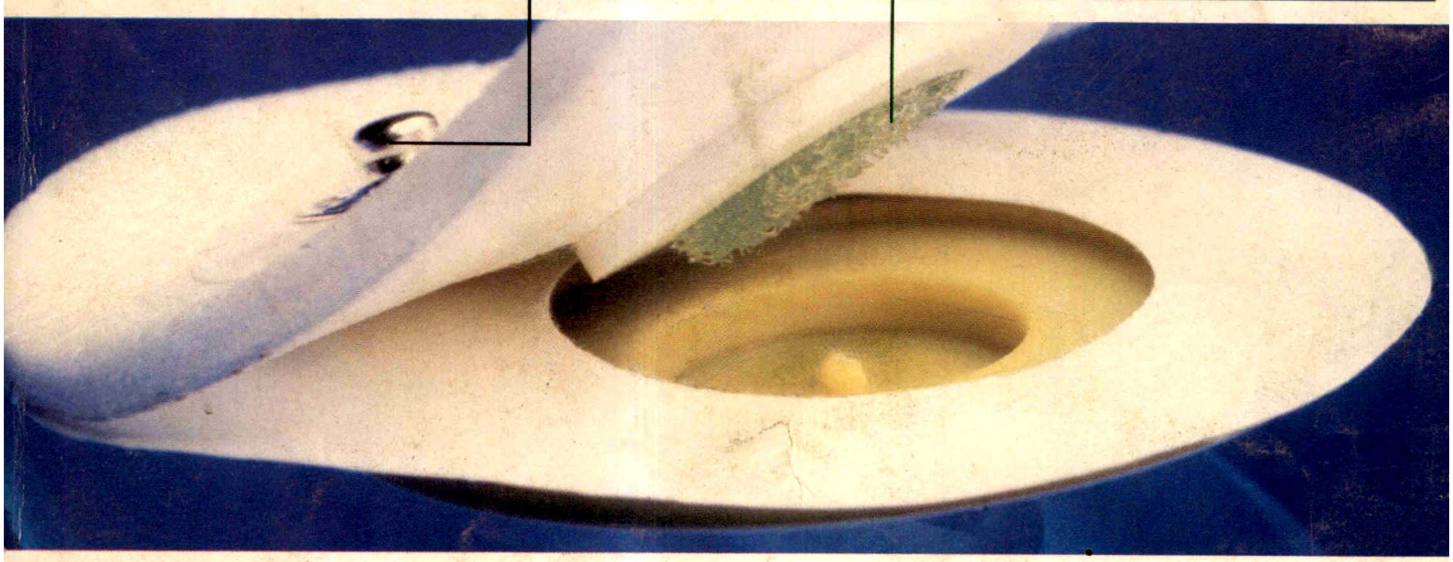
Uninterrupted ECG monitoring is virtually assured.

**Unround to result in a superior trace.**
The soft, flexible gel ring maintains a stable gel column, even during patient and/or leadwire movement. Motion artifact is greatly reduced. Further, the specially formulated low impedance gel ensures base-line stability and minimizes patient skin irritations. The result? A rapid, strong, clear trace that's trouble free.









**›ffset Dx…all the benefits ›f Offset ECG monitoring ›lectrodes…Plus**
- ›maller in size, maximizing site ›lacement flexibility
- ›ore "aggressive" adhesive, ›nportant with problem patients ›nd procedures
- ›uitable for diaphoretic patients, ›ress test and Holter Moni›ring™** procedures

**Unround Offset and Offset Dx…part of a total ECG monitoring system.**
Packaged for your convenience, Offset electrodes are available in singles, 3's and 25's. Offset Dx electrodes come in singles, 5's and 25's. A multiple layer foil package maintains a clean product that is virtually impervious to moisture/vapor transmission.

Offset and Offset Dx are part of our total ECG monitoring system that includes a complete line of cables, leadwires, recording charts and patient record forms.

**GRAPHIC CONTROLS**
*Medical Products Division*

Graphic Controls Corporation
P.O. Box 1274
Buffalo, New York 14240
716/853-7500

›anufactured under U.S. patent 3,977392
›rademark of DelMar Avionics

Copyright © 1979 Graphic Controls Corporation
All rights reserved.

ISSN 0003-2999
vol. 59, no. 5 May 1980

Acc.
6.10.80

# Anesthesia and Analgesia

Journal of the International
Anesthesia Research Society

OLDEST PUBLICATION IN THE SPECIALTY–
ESTABLISHED 1922

COLLEGE OF MEDICINE
LIBRARY

# We've just improved your esophageal stethoscope...

Digital display
for at-a-glance
convenience

## we've added temperature

National Catheter's esophageal stethoscope lets you monitor heart and respiratory sounds and now core temperature with one intubation. Temperature probe wires embedded in separate lumens can't interfere with sound transmission. Unique design gives you positive connections. Economical thermocouple design for truly affordable single use.

The hi-lo® temperature monitor has an easy-to-read digital display—no squinting at tiny numbers on a meter. The monitor does not need any "red-line" adjustment or calibration prior to each use. Ordinary D-cell batteries give you accurate readings for over 6 months of normal usage without recharging; a warning signal tells you when they need replacing.

**For more information** about the esophageal stethoscope and hi-lo® temperature monitor, get in touch with your National Catheter representative. If you use an esophageal stethoscope at all, you might as well get all the information it can give you.

See product information prior to use.

**national catheter co.**

A DIVISION OF Mallinckrodt® INC.

Hook Road, Argyle, New York 12809
Phone (518) 638-8232

# Anesthesia and Analgesia

Journal of the
International Anesthesia Research Society

3645 Warrensville Center Road
Cleveland, Ohio 44122
Telephones (216) 295-1124, 295-1130

EDITORIAL BOARD

**Editor in Chief:**
**Nicholas M. Greene, M.D.,** New Haven, Connecticut

**Editors:**
**D. Ryan Cook, M.D.,** Pittsburgh, Pennsylvania
**Douglas B. Craig, M.D.,** Winnipeg, Manitoba
**E. Paul Didier, M.D.,** Rochester, Minnesota
**Ronald W. Dunbar, M.D.,** Atlanta, Georgia
**Alison B. Froese, M.D.,** Toronto, Ontario
**John P. Kampine, M.D.,** Milwaukee, Wisconsin
**David E. Longnecker, M.D.,** Charlottesville, Virginia
**John J. Savarese, M.D.,** Boston, Massachusetts
**N. Ty Smith, M.D.,** San Diego, California
**Robert K. Stoelting, M.D.,** Indianapolis, Indiana

**Book Review Editor:**
**E. Paul Didier, M.D.,** Rochester, Minnesota

**ANESTHESIA AND ANALGESIA** (ISSN 0003-2999) is published monthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, M.D., Bruce F. Cullen, M.D., E. Paul Didier, M.D., Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., B. B. Sankey, M.D., and Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris T. Nicholson, M.D., and T. H. Seldon, M.D.

**EDITORIAL CORRESPONDENCE** and manuscripts should be addressed to: **Nicholas M. Greene, M.D., Editor in Chief, Anesthesia and Analgesia, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: [203] 436-2887).** For information concerning preparation of manuscripts see "A Guide for Authors" published in each issue. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

**BOOKS FOR REVIEW** should be sent directly to the Book Review Editor, **E. Paul Didier, M.D., ℅ Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55901.**

**REPRINTS:** For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

**BUSINESS CORRESPONDENCE,** including subscription and membership payments, single issue purchases, change of address notices and requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122 (Telephones: [216] 295-1124, 295-1130).**

**SUBSCRIPTION RATES:** United States and U.S. possessions, $30.00 per year (12 issues); all other countries, $33.00.

**MEMBERSHIP DUES (Including Journal Subscription):** United States and U.S. possessions, $30.00 per year; all other countries, $33.00. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). **Educational Membership** (half the full price) available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only, upon completion of application including certification by applicant's program director.

**SINGLE ISSUES:** $5.50 each beginning 1979; $4.50 for years 1970–1978; $3.00 for years 1954–1969; $2.00 for years 1928–1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

**MAILING DATES:** Journals mailed 25th of month preceding issue date. Second class postage paid at Cleveland, Ohio and at additional mailing offices.

**CHANGE OF ADDRESS NOTICES:** Send to Cleveland business office as much in advance as possible to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable. POSTMASTER: Send address changes to Anesthesia and Analgesia, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

**ADVERTISING:** Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086 (Telephone: [609] 848-1000). Orders, contracts, and classified ad copy should be sent to the Cleveland office. Reproduction materials and inserts should be sent to Waverly Press, Inc., 300 Idlewild Avenue, Easton, Maryland 21601.

© 1980, International Anesthesia Research Society.

COLLEGE OF MEDICINE
LIBRARY
UNIVERSITY

# Anesthesia and Analgesia

## EDITORIAL

**A Stressful Situation**—Wingard DW . . . . . . . . . . 321

## SCIENTIFIC ARTICLES

**Pulmonary and Systemic Vascular Responses to Nitrous Oxide in Patients with Mitral Stenosis and Pulmonary Hypertension**—Hilgenberg JC, McCammon RL, and Stoelting RK . . . . . . . . . . 323

**In Vivo Changes in Canine Ventricular Cardiac Conduction during Halothane Anesthesia**—Turner LA, Zuperku EJ, Purtock RV, and Kampine JP . . . . . . . . . . 327

**Dextran-Local Anesthetic Interactions**—Scurlock JE, and Curtis BM . . . . . . . . . . 335

**Changes in Respiratory Pattern Affect Dead Space/Tidal Volume Ratio during Spontaneous but not during Controlled Ventilation: A Study in Pediatric Patients**—Rose DK, and Froese AB . . . . . . . . . . 341

**Bronchofiberscopic Jet Ventilation**—Satyanarayana T, Capan L, Ramanathan S, Chalon J, and Turndorf H . . . . . . . . . . 350

**Cardiovascular Effects of Anesthetic Induction with Ketamine**—Waxman K, Shoemaker WC, and Lippmann M . . . . . . . . . . 355

**Assessment of Vaporizer Performance in Low-Flow and Closed-Circuit Anesthesia**—Lin C-Y . . . . . . . . . . 359

**Hospital Admission Blood Pressure: A Predictor for Hypertension following Endotracheal Intubation**—Bedford RF, and Feinstein B . . . . . . . . . . 367

**Assessment of Block of the Sciatic Nerve in the Popliteal Fossa**—Rorie DK, Byer DE, Nelson DO, Sittipong R, and Johnson KA . . . . . . . . . . 371

## CLINICAL REPORTS

**Human Malignant Hyperthermia: Awake Episodes and Correction by Dantrolene**—Gronert GA, Thompson RL, and Onofrio BM . . . . . . . . . . 377

**Mitral Valve Prolapse**—Krantz EM, Viljoen JF, Schermer R, and Cañas MS . . . . . . . . . . 379

**Herpangina in an Anesthesiologist**—Rosenblatt RM, and Domb GH . . . . . . . . . . 384

**Acute Myocardial Ischemia Caused by Mediastinal Chest Tube Suction**—Chapin JW, Kahre J, and Newland M . . . . . . . . . . 386

**Chemodectoma Diagnosed by Hypertension and Tachycardia during Anesthesia**—Newland MC, and Hurlbert BJ . . . . . . . . . . 388

# Contents

May 1980
Vol. 59/No. 5

**Anesthetic Considerations in Pregnant Patients Receiving Terbutaline Therapy**—Ravindran R, Viegas OJ, Padilla LM, and LaBlonde P . . . . . . 391

## LETTERS TO THE EDITORS

**Pancuronium and Gentamicin Interaction in Patients with Renal Failure**—Regan AG, and Perumbetti PPV . . . . . . 393

**Failure of a Cephalothin Test Dose to Produce Anaphylaxis**—Zeok SS, and Tsueda K . . . . . . 393

**Anticoagulants and Continuous Epidural Anesthesia**—McCullough JD; reply by Stanley TH, Lunn JK . . . . . . 394

## BOOK REVIEWS

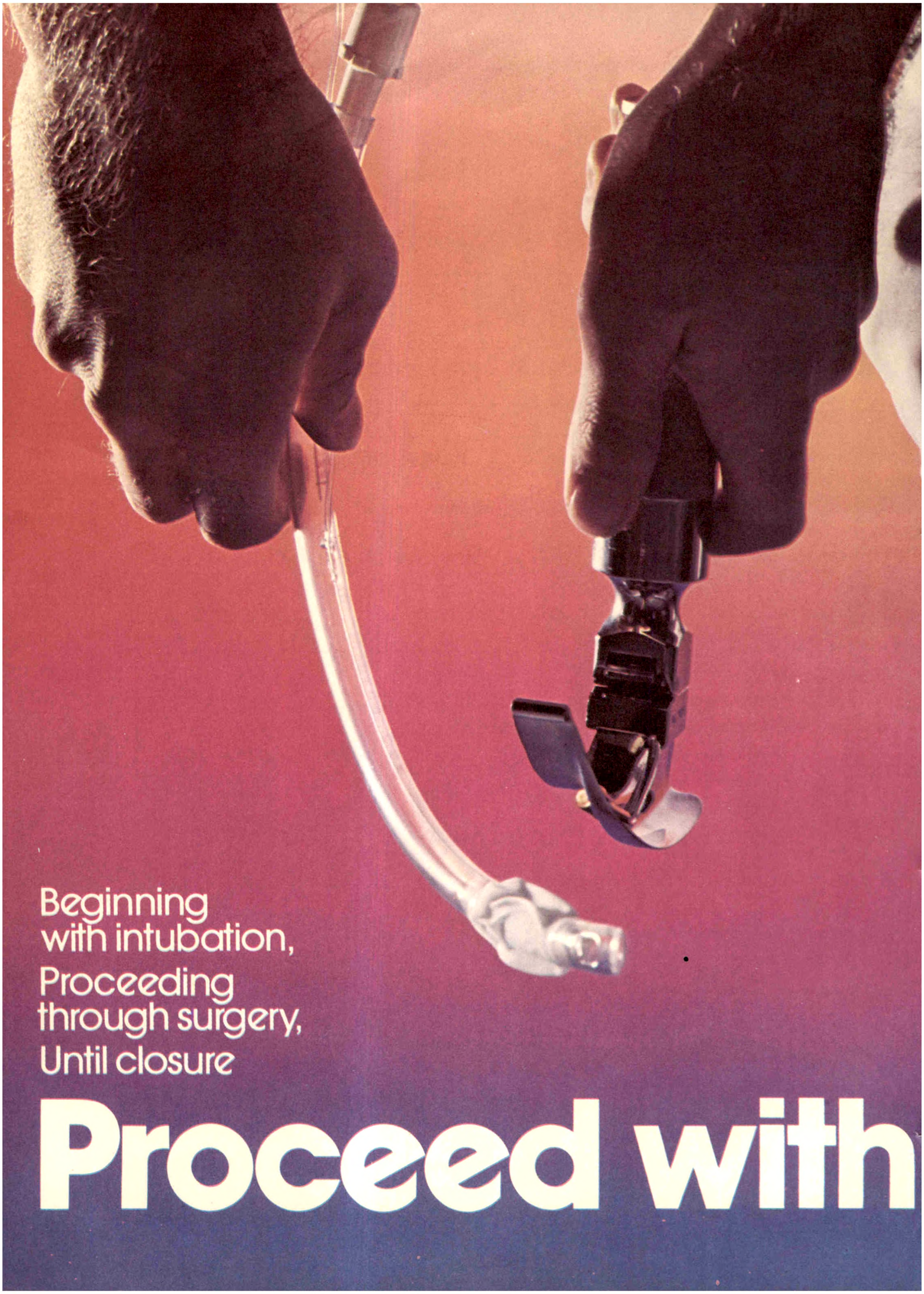
**Renal Function in Anaesthesia and Surgery**—Bevan DR . . . . . . 396

**International Anesthesiology Clinics, Volume 17**—Britt BA (Ed) . . . . . . 396

**Anaesthesia for Children**—Brown TCK, and Fisk GC . . . . . . 397

**Acupuncture Manual, A Western Approach**—Chu LSW, Yeh SDJ, and Wood DD . 397

**Blood Gases and Acid-Base Physiology**—Jones NL . . . . . . 397


Beginning
with intubation,
Proceeding
through surgery,
Until closure
Proceed with

Pavulon facilitates intubation and provides safe, neuromuscular blockade.

Histamine release and ganglionic blockade are rarely, if ever, seen.[1]

Organon

A PART OF Akzona INC.

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# PAVULON®

pancuronium bromide

Until closure

**Proceed with PAVULON®**

pancuronium bromide

The clinically proven nondepolarizing muscle relaxant

**Brief Summary** (Please consult full package insert, enclosed in every package, before using Pavulon).

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

**CAUTION:** Federal law prohibits dispensing without prescription.

**Reference:**
1. Stanley and Liu, Anesth Analg 56:669, 1977

Organon

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

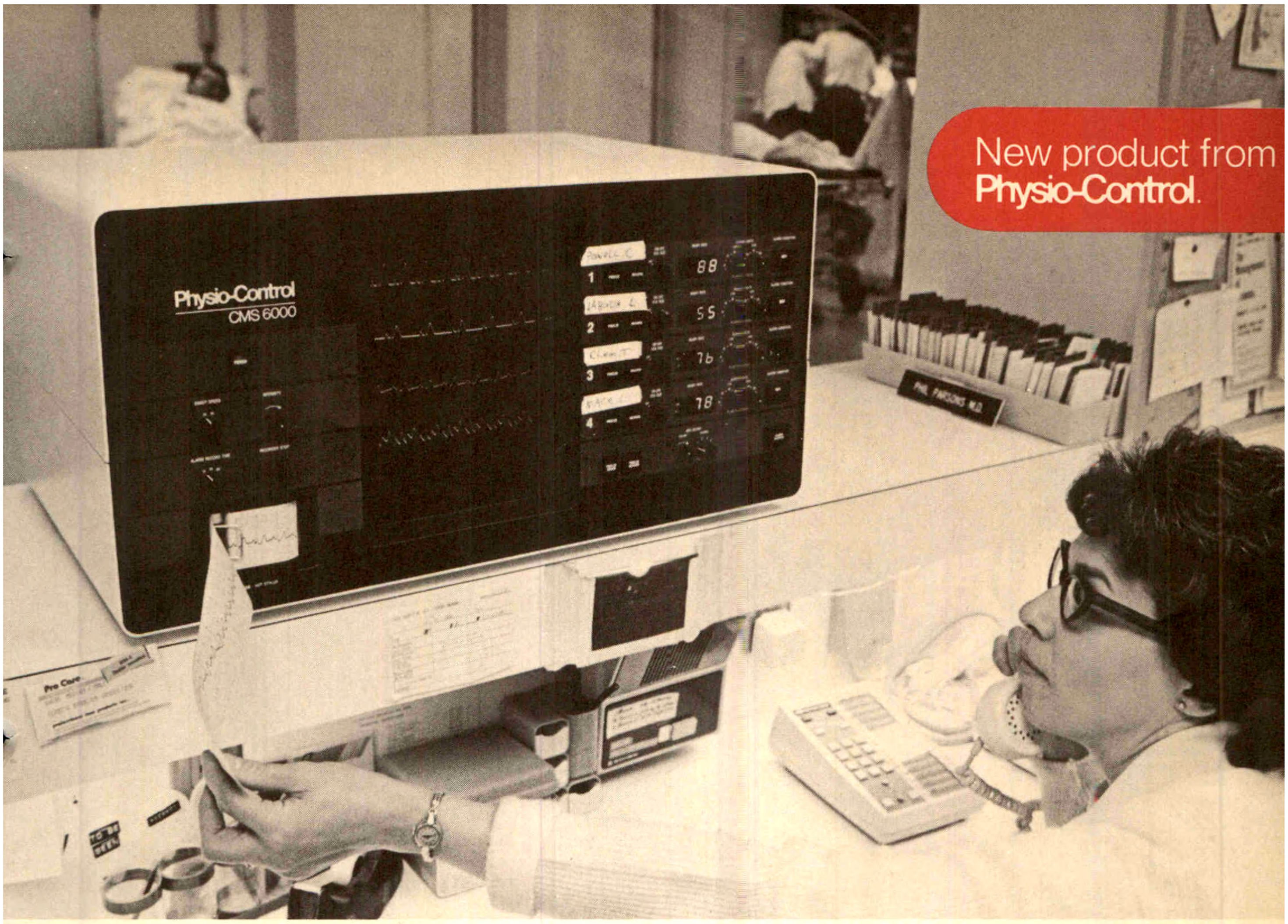
**MULTIPLE SCLEROSIS IS OF VITAL CONCERN TO EVERYONE WHO LIVES HERE.**

In our world today, an estimated one and a half million young adults are victims of multiple sclerosis. A mysterious, debilitating crippler for which there is no known cause or cure that seemingly comes from nowhere to strike at young people in their prime years.

There used to be no help, no hope. But through the efforts of the National Multiple Sclerosis Society, and the contributions of caring people, a massive research program is under way. Many feel the answer is closer than ever before. And we can find it, with your help. A major health problem, multiple sclerosis is a greater crippler than polio ever was. It should not exist in our world today.

MS

**National Multiple Sclerosis Society**
**257 Park Avenue South**
**New York, New York 10010**



# Now! A common-sense monitoring system that's flexible, functional, reliable and affordable!

Presenting the all-new Physio-Control CMS 6000—the common-sense four-bed central ECG monitoring system. We designed it specifically for the busy Emergency Department or Recovery Room. It's also ideal for the small-hospital CCU or ICU.

FUNCTIONAL—Four-channel cardioscope with freeze channel and recorder. Digital rate meters with high and low alarm limits.

FLEXIBLE—Use with portable Lifepak® 6 monitors as hardwired bedside monitors. Or all channels can be telemetry. Or any combination.

RELIABLE—The CMS is engineered and built with thoroughly-proven, highly-reliable electronic components. And the system is backed by Physio-Control's own nationwide factory service team.

AFFORDABLE—Because we engineered it to deliver only the *most needed* functions, the CMS 6000 gives you more function at lower cost.

That's the whole idea. That's common sense. That's the CMS 6000.

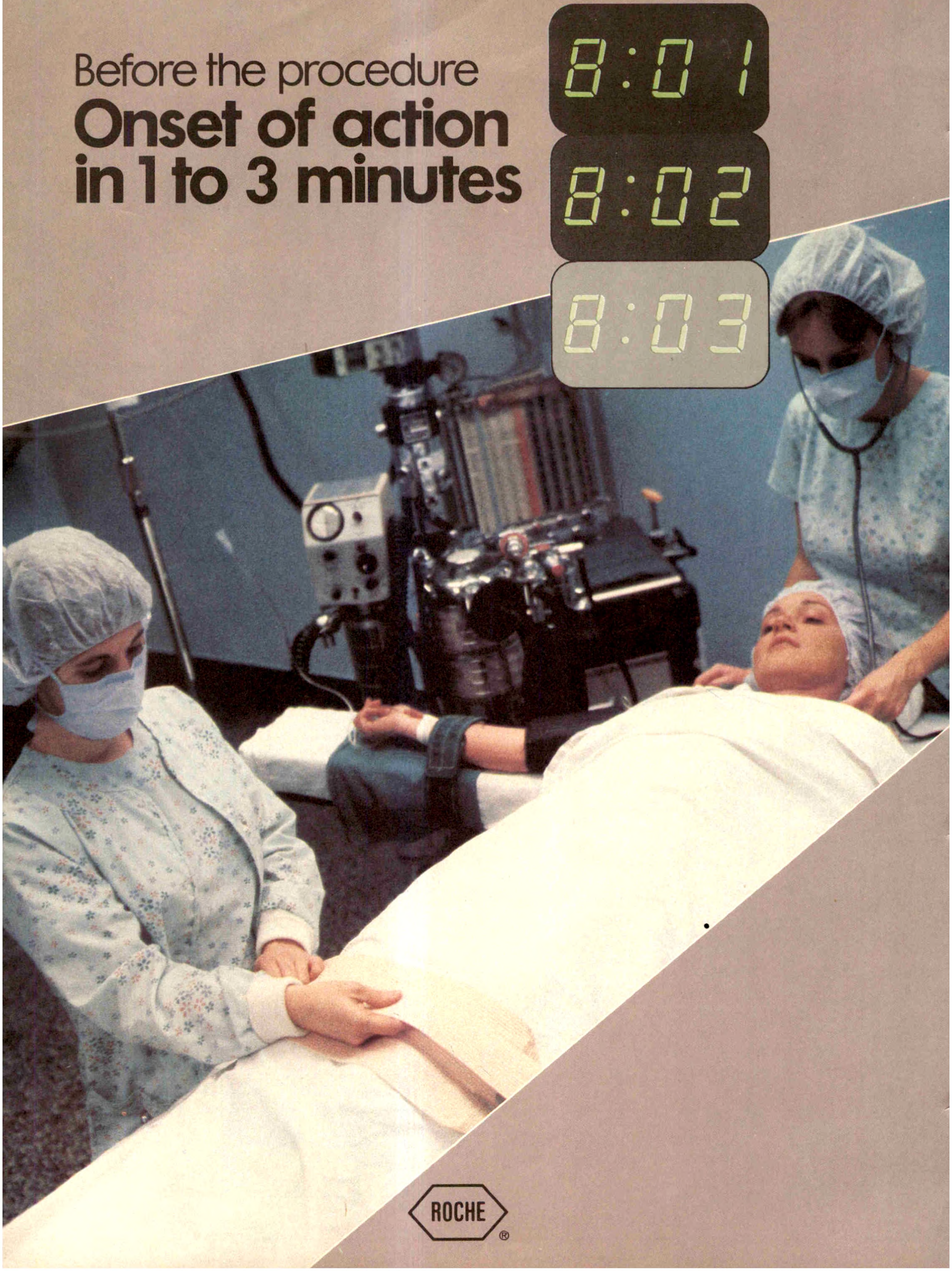
The new CMS 6000
from **Physio-Control**

---

**Physio-Control** is the world leader in acute cardiac care systems. 11811 Willows Road, Redmond, Washington 98052
(206) 881-4000/U.S. Telex: 32-0268 International Telex: 32-0166

Before the procedure

## Onset of action in 1 to 3 minutes



ROCHE ®

# After the procedure
# **Diminished recall**

## Preoperative relief with postoperative benefits

☐ Predictable course of action—onset within minutes, release within hours. As with most CNS-acting drugs, outpatients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, *e.g.*, operating machinery or driving.

☐ Calm relaxed patient, better prepared for the procedure.

☐ A proven record of safety and performance.

☐ Does not normally compromise cardiac or respiratory function. Resuscitative equipment should be readily available.

☐ Use with care in elderly, very ill and patients with limited pulmonary reserve (see Warnings section on following page).

☐ Narcotic dosage can and should be reduced.

**Injectable Valium® I.V.**
diazepam/Roche Ⓒ IV

A pattern of action
that meets your needs

**Please see summary of product information on next page.**

## New/Improved
# Tel-E-Ject®
## 10-mg Disposable Syringe (5 mg/ml)

scale on both sides of barrel eases visibility during administration

## Injectable
# Valium® I.V.
## diazepam/Roche

10-ml vials } 5 mg/ml
2-ml ampuls }

**Please consult complete product information, a summary of which follows:**

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

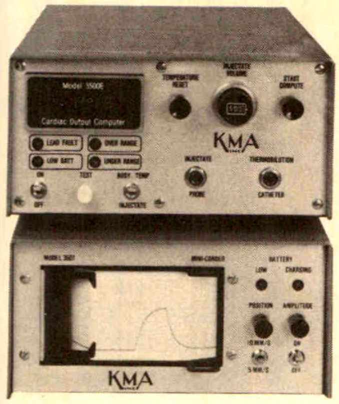
**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE®
ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

## THERMODILUTION CARDIAC OUTPUT COMPUTER



**MODEL 3500E**

Latest bedside cardiac output computer monitoring technology.

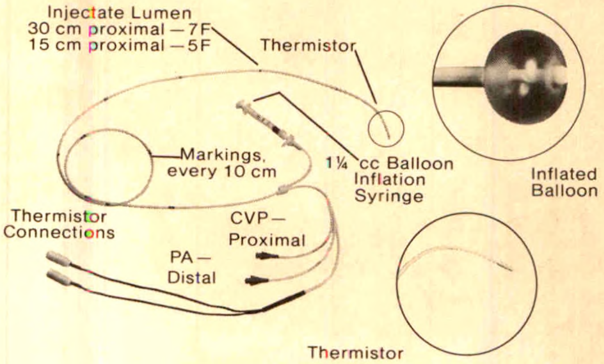
**MODEL 3501**

Companion automatic recorder for thermodilution curve.

**Features:**

- ACCURATE cardiac outputs — adult and pediatric ranges
- SIMPLE pushbutton operation
- ADJUSTABLE test calibration
- AUTOMATIC body and injectate temperatures
- AUTOMATIC thermal curve recording
- CHOICE of injectate volume and temperature
- SERVICEABLE — interchangeable circuitry

## THERMODILUTION CATHETERS



**Features:**

- Convenient and complete sterile packaging
- Precalibrated and interchangeable
- Adult, pediatric and direct placement sizes
- Tapered tip — pressure fidelity and introduction
- Thermistor located inside J curve — prevents P.A. wall contact
- Balloon protection shield

KMA INC

For Additional Information, contact Ross Linnemann
**KMA, INC.**
150 Coolidge Avenue
Watertown, Massachusetts 01172
(800) 225-3080
In Mass. call: (617) 926-6151

## *I.A.R.S. 1980*
## *REVIEW COURSE LECTURES*
## AND
## *ABSTRACTS OF SCIENTIFIC PAPERS*

200-page booklet including 16 Review Course Lectures and Abstracts of 62 scientific papers given at the IARS 54th Congress, March 10–13, 1980. Copies available now from IARS Cleveland office - $5.00 per copy.

I.A.R.S.
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Enclosed is check for $______ for ______ copy(ies) of "1980 Review Course Lectures" to be sent to:

(name)

(Mail address)

(City-state-zip)

SIEMENS

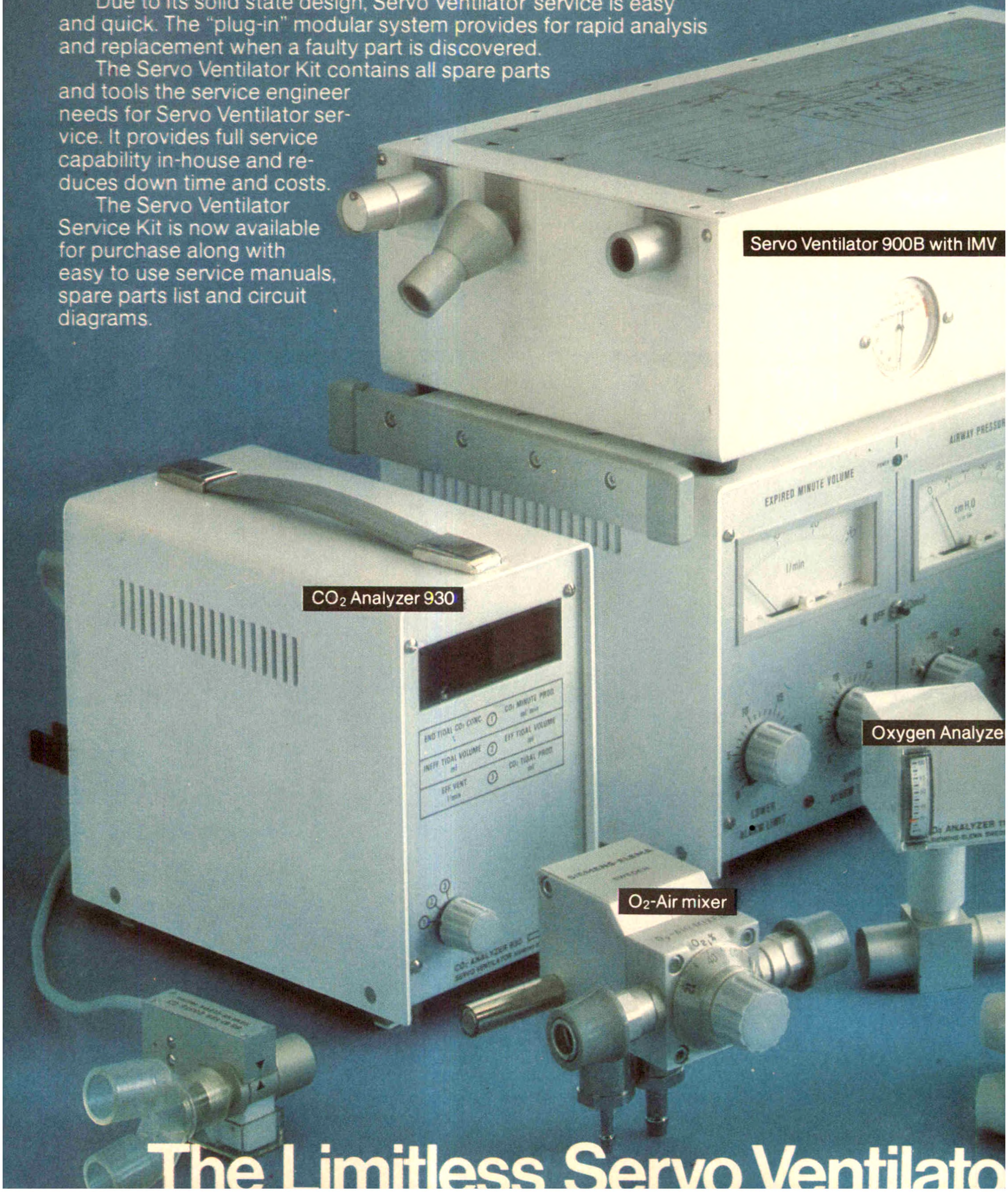
# Servo Ventilator Service

Though Siemens has a vast service organization throughout the world, it is seldom you need to call them for Servo Ventilator products.

Due to its solid state design, Servo Ventilator service is easy and quick. The "plug-in" modular system provides for rapid analysis and replacement when a faulty part is discovered.

The Servo Ventilator Kit contains all spare parts and tools the service engineer needs for Servo Ventilator service. It provides full service capability in-house and reduces down time and costs.

The Servo Ventilator Service Kit is now available for purchase along with easy to use service manuals, spare parts list and circuit diagrams.



Servo Ventilator 900B with IMV

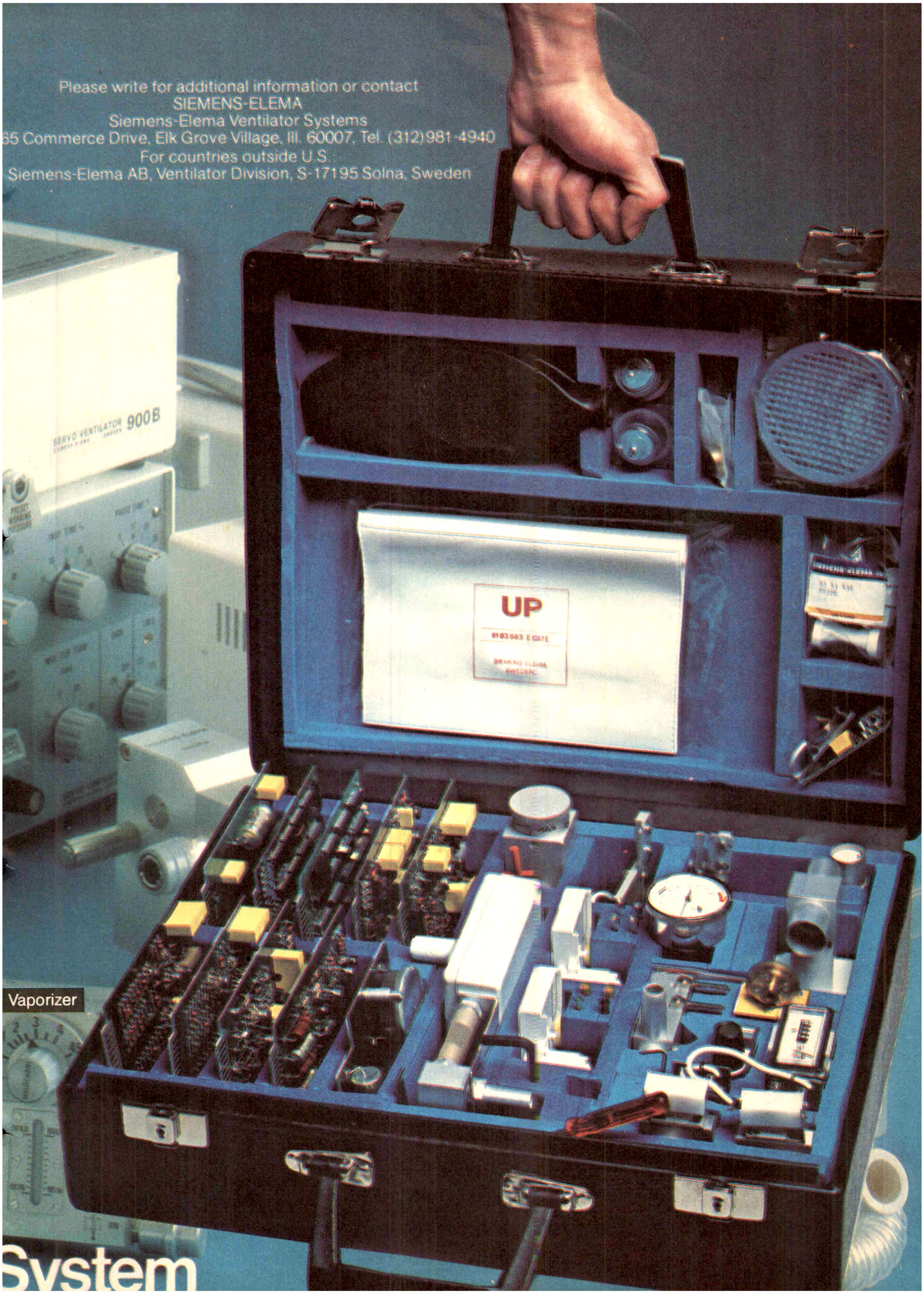
CO$_2$ Analyzer 930

Oxygen Analyze

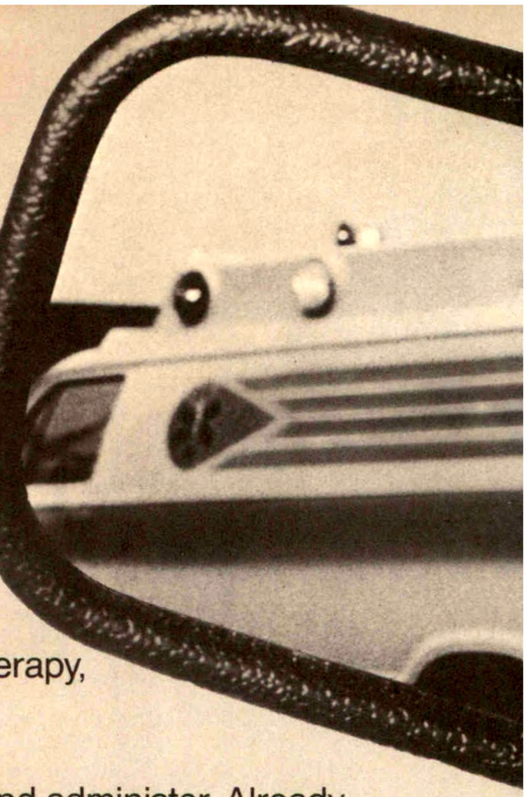
O$_2$-Air mixer

## The Limitless Servo Ventilato

Please write for additional information or contact
SIEMENS-ELEMA
Siemens-Elema Ventilator Systems
65 Commerce Drive, Elk Grove Village, Ill. 60007, Tel. (312) 981-4940
For countries outside U.S.:
Siemens-Elema AB, Ventilator Division, S-171 95 Solna, Sweden



# CORTICOID THERAPY IN CRITICAL CARE



Pharmacologic doses of corticoids have been used in the treatment of shock unresponsive to conventional therapy, if adrenocortical insufficiency exists or is suspected.

## Differences That Count

Hexadrol® phosphate injection is easy to handle, store and administer. Already in solution, it can be used directly from the vial. Hexadrol has benzyl alcohol as a preservative and is stable at room temperature.

The multi-dose vial minimizes waste. When used in pharmacologic doses, Hexadrol offers significant savings over methylprednisolone.*

*Based on average wholesale price listings in *Drug Topics Red Book 1979.* Actual prices paid by direct purchasers will vary by order size but are usually lower for Hexadrol.

# Hexadrol® Phosphate Injection

## dexamethasone sodium phosphate injection USP

**BEFORE PRESCRIBING OR ADMINISTERING, PLEASE CONSULT COMPLETE PRODUCT INFORMATION, A SUMMARY OF WHICH FOLLOWS:**

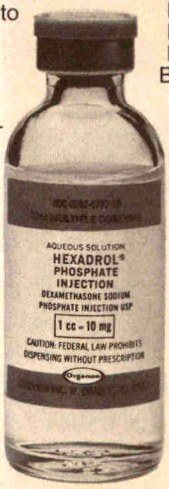
**ACTIONS**—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

**CONTRAINDICATIONS**—Systemic fungal infections—Hypersensitivity to any component.

**WARNINGS**—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

**Usage In Pregnancy.** Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be necessary.



100 mg

All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

**PRECAUTIONS**—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, approrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

**ADVERSE REACTIONS—**

**Fluid and electrolyte disturbances:** Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

**Musculoskeletal:** Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

**Gastrointestinal:** Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

**Dermatologic:** Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

**Neurological:** Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

**Endocrine:** Menstrual irregularities; Development of Cushingoid state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; Increased requirements for insulin or oral hypoglycemic agents in diabetics.

**Ophthalmic:** Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

**Metabolic:** Negative nitrogen balance due to protein catabolism.

**Miscellaneous:** Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

**DOSAGE AND ADMINISTRATION**—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

**DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.**

**CAUTION**—Federal law prohibits dispensing without prescription.

**HOW SUPPLIED**—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25; 10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

Hexadrol is available in two potencies, 4mg/cc and 10mg/cc in aqueous solution with 1% benzyl alcohol as preservative.

## When You Need it... Hexadrol Has It!

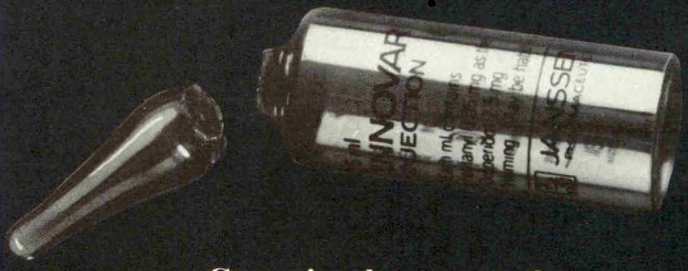
Organon

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# As an aid to induction,

# Innovar® INJECTION Ⓒ (droperidol/fentanyl)

# can help

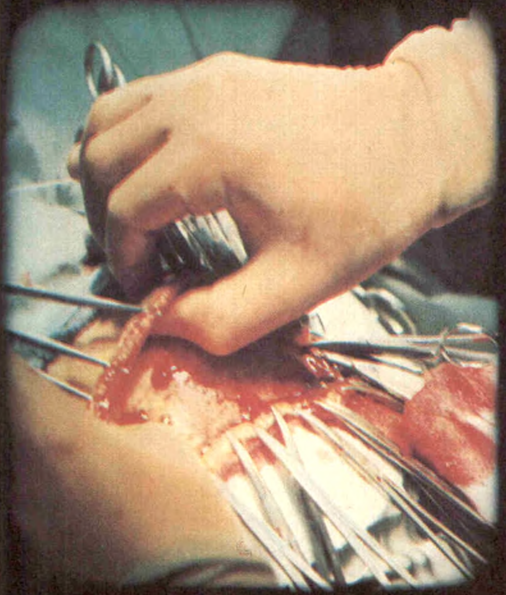


**Committed to research…**
**because so much remains to be do**

**JANSSEN PHARMACEUTICA I**
501 George Street, New Brunswick, N.J. 0

## 1. Establish a foundation of tranquility and analgesia

Smooth intubation
Minimize the need for thiopental



## 2. Foster a smooth and uneventful intraoperative course

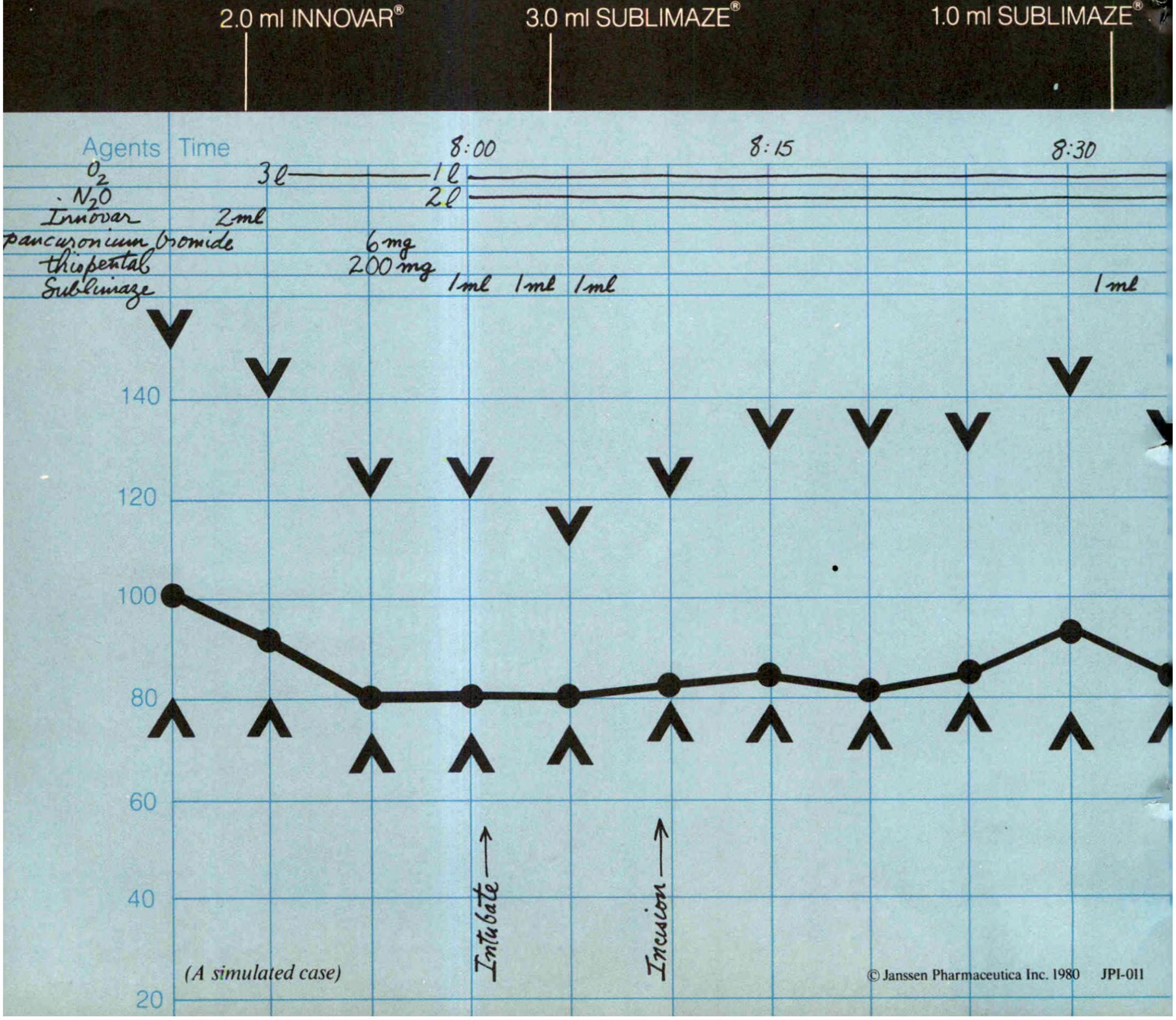
Provide an anesthetic baseline
Promote cardiovascular stability

## 3. Maintain a quiet and less troublesome postoperative period

Reduce the incidence of nausea and vomiting
Minimize the need for postoperative analgesics
Provide tranquilization and tolerance
of discomfort

**Innovar® (droperidol/fentanyl) injection Ⓒ**
**proven by a decade of worldwide experience**

# Adequate analgesia with Sublimaze® INJECTION Ⓒ (fentanyl) can help suppress surgical stress



(A simulated case)

© Janssen Pharmaceutica Inc. 1980 JPI-011

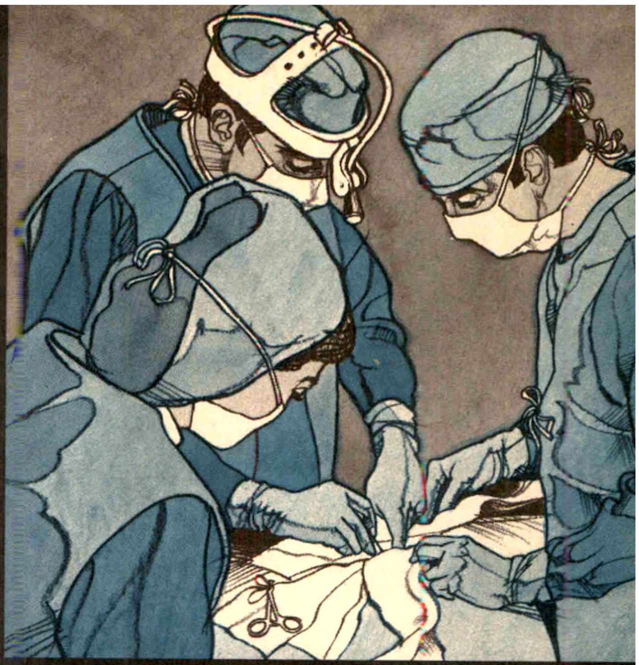
**Administered following induction, 3-5 ml of SUBLIMAZE® (fentanyl) injection Ⓒ will:**

- provide profound analgesia
- minimize catecholamine release
- lay a foundation for a smooth intraoperative course

**Used as needed during surgery, SUBLIMAZE® offers controllable analgesia:**

- rapid onset
- short duration of action*
- rapid reversibility by narcotic antagonists*
- analgesic action carries over into postoperative period*

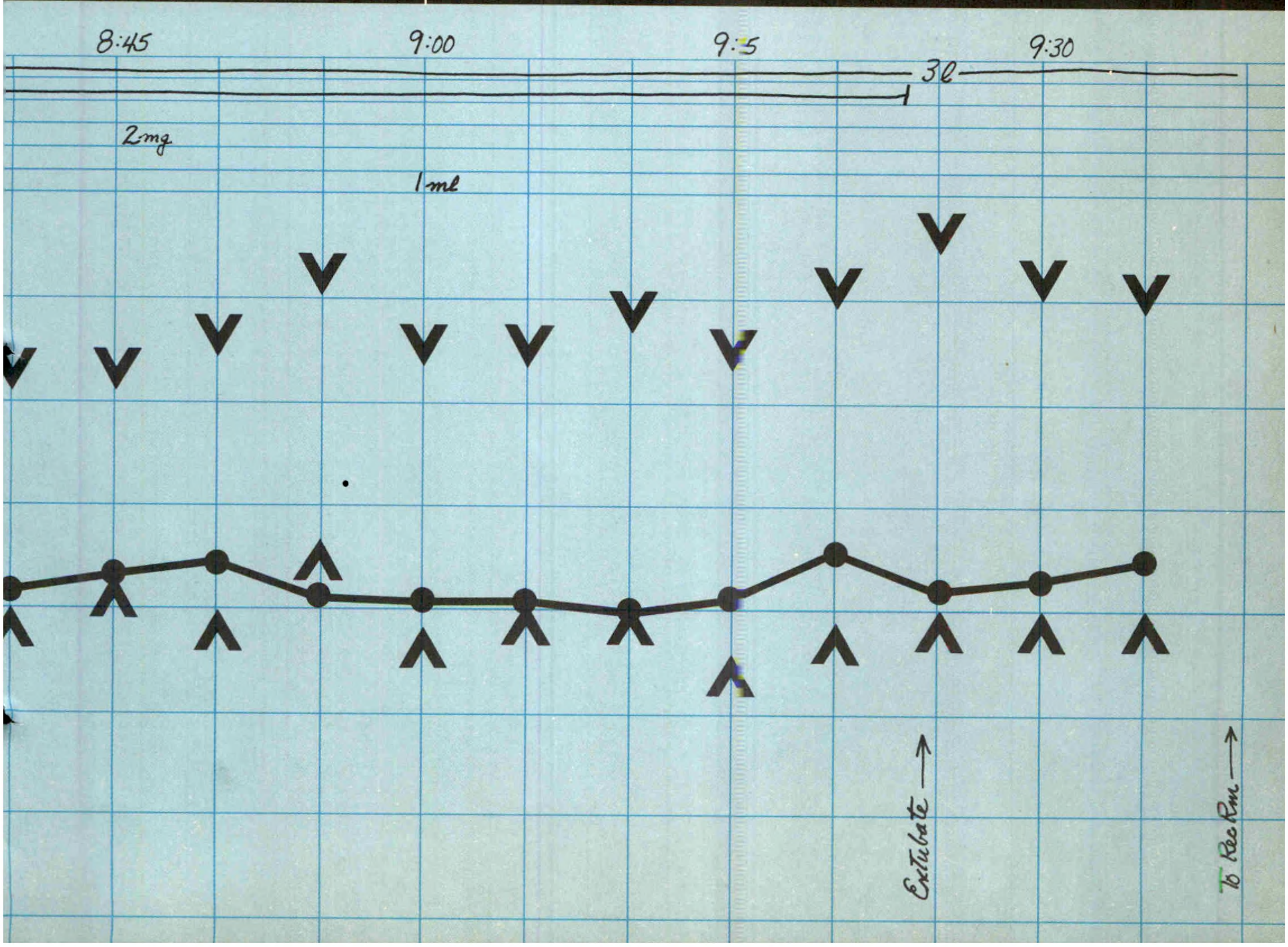
*The respiratory depressant effect of Sublimaze® (fentanyl) injection Ⓒ may last longer than the analgesic effect.



*Please see Prescribing Information on following pages*

**JANSSEN PHARMACEUTICA INC.**
501 George Street, New Brunswick, N.J. 08903

1.0 ml SUBLIMAZE®



# **Innovar**® Injection CII ℞

## FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

> The two components of INNOVAR injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

**DESCRIPTION:** Each ml. contains (in a 1:50 ratio):
Fentanyl .......... 0.05 mg.
as the citrate
*Warning:* May be habit forming
Droperidol .......... 2.5 mg.
Lactic acid for adjustment of pH to 3.5 ± 0.3

**ACTIONS:** INNOVAR injection is a combination drug containing a narcotic analgesic, fentanyl, and a neuroleptic (major tranquilizer), droperidol. The combined effect, sometimes referred to as neuroleptanalgesia, is characterized by general quiescence, reduced motor activity, and profound analgesia; complete loss of consciousness usually does not occur from use of INNOVAR injection alone. The incidence of early postoperative pain and emesis may be reduced.

A. Fentanyl is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. Fentanyl in a dose of 0.1 mg. (2.0 ml.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays, and skin wheal testing in man, as well as *in vivo* testing in dogs indicate that histamine release rarely occurs with fentanyl.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single I.V. dose of up to 0.1 mg. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is from one to two hours.

As with longer-acting narcotic analgesics, the duration of the respiratory depressant effect of *SUBLIMAZE* (fentanyl) may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to $CO_2$ stimulation following administration of fentanyl to man:

1. DIMINISHED SENSITIVITY TO $CO_2$ STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE. Fentanyl frequently slows the respiratory rate but this effect is seldom noted for over 30 minutes regardless of the dose administered.
2. Duration and degree of respiratory depression is dose related.
3. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.
4. Altered sensitivity to $CO_2$ stimulation has been demonstrated for up to four hours following a single intravenous dose of 0.6 mg. (12 ml.) fentanyl to healthy volunteers.

See also WARNINGS and PRECAUTIONS concerning respiratory depression.

B. Droperidol produces marked tranquilization and sedation. It also produces an antiemetic effect as evidenced by the antagonism of apomorphine in dogs. It potentiates other CNS depressants. It also produces mild alpha-adrenergic blockade, peripheral vascular dilatation and reduction of the pressor effect of epinephrine. Droperidol can produce hypotension and decreased peripheral vascular resistance. It may decrease pulmonary arterial pressure (particularly if it is abnormally high). It may reduce the incidence of epinephrine-induced arrhythmias but it does not prevent other cardiac arrhythmias. The onset of action is from three to ten minutes following intravenous or intramuscular administration. The full effect, however, may not be apparent for 30 minutes. The duration of the sedative and tranquilizing effects generally is two to four hours. Alteration of consciousness may persist as long as 12 hours. This is in contrast to the much shorter duration of fentanyl.

**INDICATIONS:** INNOVAR injection is indicated to produce tranquilization and analgesia for surgical and diagnostic procedures. It may be used as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia. If the supplementation of analgesia is necessary, *SUBLIMAZE®* (fentanyl) injection alone rather than the combination drug INNOVAR injection, should usually be used; see Dosage and Administration Section.

**CONTRAINDICATIONS:** INNOVAR injection is contraindicated in patients with known intolerance to either component.

**WARNINGS:** AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.
See also discussion of narcotic antagonists in PRECAUTIONS and OVERDOSAGE.
FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

*The respiratory depressant effect of narcotics persists longer than the measured analgesic effect. When used with* INNOVAR *injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended.*

INNOVAR injection *may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.*

***Drug Dependence:*** *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of INNOVAR injection or *SUBLIMAZE* (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

***Head Injuries and Increased Intracranial Pressure:*** INNOVAR injection should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, INNOVAR injection may obscure the clinical course of patients with head injury.

***Usage in Children:*** The safety of INNOVAR injection in children younger than two years of age has not been established.

***Usage in Pregnancy:*** The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

**PRECAUTIONS:** *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilation and hypotension because of sympathetic blockade. Through other mechanisms (see Actions), fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in the moving and positioning of patients because of a possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and *SUBLIMAZE* (fentanyl), should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperative respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl (as *SUBLIMAZE* (fentanyl) or INNOVAR) employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection, the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

**ADVERSE REACTIONS:** The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INNOVAR injection. Restlessness, hyperactivity and anxiety which can be either the result of inadequate tranquilization or part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-Parkinson agents.

Elevated blood pressure, with and without preexisting hypertension, has been reported following administration of INNOVAR injection. This might be due to unexplained alterations of sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, laryngospasm, bronchospasm, bradycardia, tachycardia, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

**DOSAGE AND ADMINISTRATION:** *Dosage should be individualized.* Some of the factors to be considered in determining dose are age, body weight, physical status, underlying pathological condition, use of other drugs, the type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Most patients who have received INNOVAR injection do not require narcotic analgesics during the immediate postoperative period. It is recommended that narcotic analgesics, when required, be used initially in reduced doses, as low as ¼ to ⅓ those usually recommended.

***Usual Adult Dosage:***

I. *Premedication*—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—0.5 to 2.0 ml. may be administered *intramuscularly* 45 to 60 minutes prior to surgery with or without atropine.

II. *Adjunct to General Anesthesia–Induction*—1 ml. per 20 to 25 pounds of body weight, may be administered slowly intravenously. Smaller doses may be adequate.
The total amount of INNOVAR injection administered should be carefully titrated to obtain the desired effect based on the individual patient's response.

There are several methods of administration of INNOVAR injection for induction of anesthesia.

A. Intravenous injection—To allow for the variable needs of patients INNOVAR injection may be administered intravenously in fractional parts of the calculated dose. With the onset of somnolence, the general anesthetic may be administered.

B. Intravenous drip—10 ml. of INNOVAR injection are added to 250 ml. of 5% dextrose in water and the drip given rapidly until the onset of somnolence. At that time, the drip may be either slowed or stopped and the general anesthetic administered.

*Maintenance*—INNOVAR injection is not indicated as the sole agent for the maintenance of surgical anesthesia. It is customarily used in combination with other measures such as nitrous oxide-oxygen, other inhalation anesthetics, and/or topical or regional anesthesia.

To prevent the possibility of excessive accumulation of the relatively long-acting droperidol component, *SUBLIMAZE* (fentanyl) alone should be used in increments of 0.025 to 0.05 mg. (0.5 to 1.0 ml.) for the maintenance of analgesia in patients initially given INNOVAR injection as an adjunct to general anesthesia. (See *SUBLIMAZE* (fentanyl) package insert for additional prescribing information.) However, in prolonged operations, additional 0.5 to 1.0 ml. amounts of INNOVAR injection may be administered with caution intravenously if changes in the patient's condition indicate lightening of tranquilization and analgesia.

III. *Use Without a General Anesthetic in Diagnostic Procedures*—Administer the usual I.M. premedication (0.5 to 2.0 ml.) 45 to 60 minutes before the procedure. To prevent the possibility of excessive accumulation of the relatively long-acting droperidol component, *SUBLIMAZE* (fentanyl) alone should be used in increments of 0.025 to 0.05 mg. (0.5 to 1.0 ml.) for the maintenance of analgesia in patients initially given INNOVAR injection. (See *SUBLIMAZE* (fentanyl) package insert for additional information). However, in prolonged operations, additional 0.5 to 1.0 ml. amounts of INNOVAR injection may be administered with caution intravenously if changes in the patient's condition indicate lightening of tranquilization and analgesia.

Note: When INNOVAR injection is used in certain procedures such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. *Adjunct to Regional Anesthesia*—1 to 2 ml. may be administered intramuscularly or slowly intravenously when additional sedation and analgesia are required.

***Usual Children's Dosage:***

I. *Premedication*—0.25 ml. per 20 lbs. body weight administered *intramuscularly* 45 to 60 minutes prior to surgery with or without atropine.

II. *Adjunct to General Anesthesia*—The total combined dose for induction and maintenance averages 0.5 ml. per 20 lbs. body weight. Following induction with INNOVAR injection, *SUBLIMAZE* (fentanyl) alone in a dose of ¼ to ⅓ that recommended in the adult dosage section should usually be used when indicated to avoid the possibility of excessive accumulation of droperidol. However, in prolonged operations, additional increments of INNOVAR injection may be administered with caution when changes in the patient's condition indicate lightening of tranquilization and analgesia.

See Warnings and Precautions for use of INNOVAR injection with other CNS depressants, and in patients with altered response.

**OVERDOSAGE:** ***Manifestations:*** The manifestations of INNOVAR injection overdosage are an extension of its pharmacologic actions.

***Treatment:*** In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression caused by the narcotic component fentanyl. This does not preclude the use of more immediate counter-measures. The duration of respiratory depression following overdose of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package inserts of the individual narcotic antagonists for details about use.

**HOW SUPPLIED:** INNOVAR® injection is supplied in 2 ml. and 5 ml. ampuls, in packages of 10.

U.S. Patent No. 3,141,823 Rev. 1/80

# **Sublimaze**® (fentanyl) injection Ⓒ ℞

**DESCRIPTION:** Each ml. contains:
Fentanyl .................................................. 0.05 mg.
as the citrate

*Warning:* May be habit forming.

Sodium hydroxide for adjustment of pH to 4.0-7.5.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

**ACTIONS:** SUBLIMAZE (fentanyl) is a narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. SUBLIMAZE (fentanyl) in a dose of 0.1 mg. (2.0 ml.) is approximately equivalent in analgesic activity to 10 mg. of morphine or 75 mg. of meperidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the dose of narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. SUBLIMAZE (fentanyl) appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as in *in vivo* testing in dogs, indicate that histamine release rarely occurs with SUBLIMAZE (fentanyl).

SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia, and bronchoconstriction.

The onset of action of SUBLIMAZE (fentanyl) is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single I.V. dose of up to 0.1 mg. Following intramuscular administration, the onset of action is from seven to eight minutes, and the duration of action is one to two hours. As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of SUBLIMAZE (fentanyl) may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to $CO_2$ stimulation following administration of fentanyl to man:

1. DIMINISHED SENSITIVITY TO $CO_2$ STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE. Fentanyl frequently slows the respiratory rate, but this effect is seldom noted for over 30 minutes regardless of the dose administered.
2. Duration and degree of respiratory depression is dose related.
3. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.
4. Altered sensitivity to $CO_2$ stimulation has been demonstrated for up to four hours following a single intravenous dose of 0.6 mg. (12 ml.) fentanyl to healthy volunteers.

See also WARNINGS and PRECAUTIONS concerning respiratory depression.

**INDICATIONS:** SUBLIMAZE (fentanyl) is indicated:

—for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate post-operative period (recovery room) as the need arises.
—for use as a narcotic analgesic supplement in general or regional anesthesia.
—for administration with a neuroleptic such as *INAPSINE*® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

**CONTRAINDICATIONS:** SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

**WARNINGS:** AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (FENTANYL) SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

*As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended.* SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

***Drug Dependence:*** SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

***Head Injuries and Increased Intracranial Pressure:*** SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

***Usage in Children:*** The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

***Usage in Pregnancy:*** The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

**PRECAUTIONS:** *The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol), hypotension can occur. If this occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol). When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

**ADVERSE REACTIONS:** As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without preexisting hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with INAPSINE (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** *Dosage should be individualized.* Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

***Usual Adult Dosage:***

I. *Premedication* (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—0.05 to 0.1 mg. (1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia Induction*—0.05 to 0.1 mg. (1 to 2 ml.) may be administered initially intravenously and may be repeated at 2 to 3 minute intervals until desired effect is achieved. A reduced dose as low as 0.025 to 0.05 mg. (0.5 to 1 ml.) is recommended in elderly and poor-risk patients.

*Maintenance*—0.025 to 0.05 mg. (0.5 to 1 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

If *INNOVAR*® injection is administered in addition to SUBLIMAZE (fentanyl), the calculation of the recommended dose of SUBLIMAZE (fentanyl) should include the fentanyl contained in the *INNOVAR* injection. See *INNOVAR* injection Package Insert for full prescribing information.

III. *Adjunct to Regional Anesthesia*—0.05 to 0.1 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional analgesia is required.

IV. *Postoperatively (recovery room)*—0.05 to 0.1 mg. (1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

***Usual Children's Dosage:*** For induction and maintenance in children two to 12 years of age, a reduced dose as low as 0.02 to 0.03 mg. (0.4 to 0.6 ml.) per 20 to 25 pounds is recommended. See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

**OVERDOSAGE:** ***Manifestations:*** The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

***Treatment:*** In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

**HOW SUPPLIED:** 2 ml. and 5 ml. ampuls—packages of 10.

U.S. Patent No. 3,164,600 Rev. 1/80

## Committed to research... because so much remains to be done.

ANSSEN PHARMACEUTICA INC., New Brunswick, New Jersey 08903

COLLEGE OF MEDICINE · U. C. · LIBRARY · UNIVERSITY

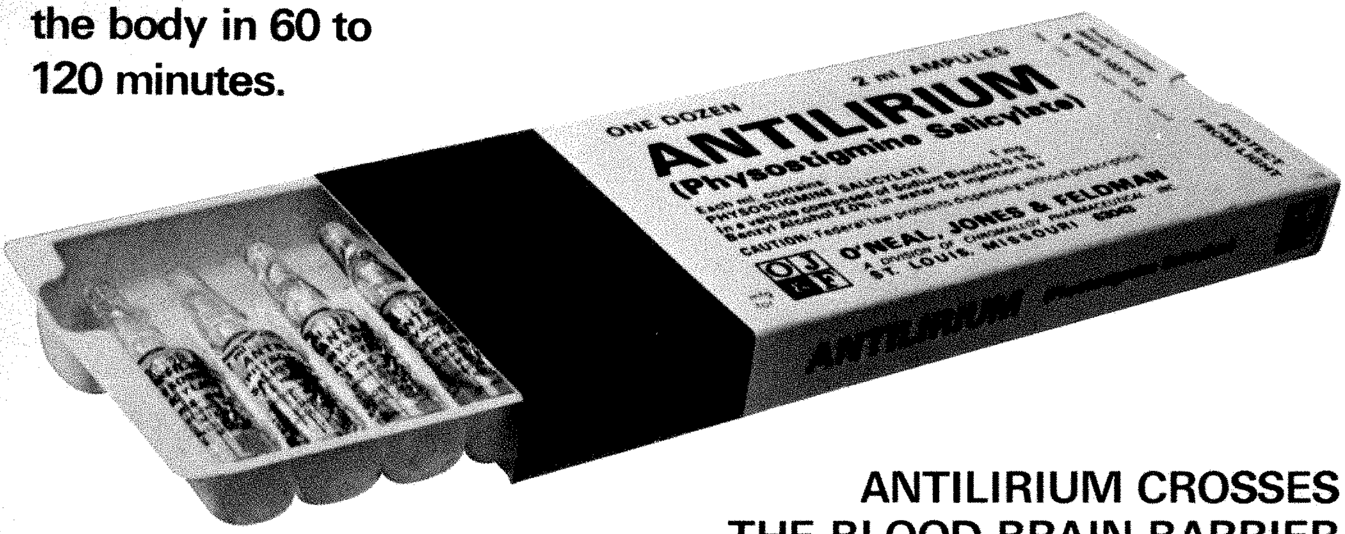
# ANTILIRIUM

## (Physostigmine Salicylate)

**QUICKLY BECOMING THE DRUG OF CHOICE FOR REVERSING PROLONGED SOMNOLENCE, DELIRIUM AND OTHER ANTICHOLINERGIC SIDE EFFECTS.**

More Anesthesiologists are relying on ANTILIRIUM because...

- Patients are revived in minutes after I.V. administration.
- Reverses anticholinergic side effects.
- Patient safety—metabolized in the body in 60 to 120 minutes.



ANTILIRIUM CROSSES THE BLOOD BRAIN BARRIER WHEREAS NEOSTIGMINE DOES NOT

ANTILIRIUM, unlike other anticholinesters including neostigmine does not have a quaternary nitrogen atom, but has a tertiary amine. For this reason it is nonionized and rapidly crosses the blood brain barrier.

OJ
&F O'NEAL, JONES & FELDMAN PHARMACEUTICALS • ST. LOUIS, MO 63043

**ANTILIRIUM**
**(Physostigmine Salicylate)**

**DESCRIPTION**: ANTILIRIUM Injection (physostigmine salicylate) is OJF's brand of physostigmine salicylate.

| | |
|---|---|
| ANTILIRIUM INJECTION | 1 mg./ml. |
| FOR INTRAMUSCULAR OR INTRAVENOUS USE | |
| Each ml. contains: | |
| PHYSOSTIGMINE SALICYLATE | 1 mg. |

In a vehicle composed of Sodium Bisulfite 0.1%, Benzyl Alcohol 2.0%; in water for injection q.s.

**ACTION**: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. The action of acetylcholine is normally very fleeting because of its hydrolysis by a specific enzyme. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine. The changes in body function which are produced by the injection of physostigmine are, therefore, very similar to those which would occur from simultaneous stimulation of the parasympathetic nerves and include contraction of the pupil, increased tonus of the intestinal musculature, constriction of the bronchi and stimulation of secretion of the salivary and sweat glands.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quarternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Drugs with anticholinergic properties primarily antagonize acetylcholine competitively at the neuroreceptor site. Cardiac muscle, exocrine glands, and smooth muscle are most markedly affected. Action of the inhibitors is overcome by increasing the level of acetylcholine naturally generated in the body through inhibiting the enzyme (cholinesterase) which normally prevents accumulation of excess acetylcholine. It does this by hydrolyzing that compound to inactive acetic acid and choline. Agents which inhibit this enzyme, so that acetylcholine accumulates at the neuroreceptor sites, are called anticholinesterases.

Physostigmine, one of the anticholine esterases which is a tertiary amine, crosses into the central nervous system and can reverse both central and peripheral anticholinergic actions.

The anticholinergic syndrome has both central and peripheral signs and symptoms. Central toxic effects include anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Severe poisoning may produce coma, medullary paralysis, and death. Peripheral toxicity is characterized by tachycardia, hyperpyrexia, mydriasis, vasodilatation, urinary retention, diminution of gastrointestinal motility, decrease of secretion in salivary and sweat glands, and loss of secretions in the pharynx, bronchi, and nasal passages.

Some drugs in the anticholinergic group, such as imipramine and related tricyclics also produce additional toxic effects such as cardiac arrhythmias which can be reversed by physostigmine.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Toxic effects from mixed drug ingestions and combination preparations such as amitriptyline and perphenazine may respond less dramatically. Since physostigmine is rapidly metabolized, therapeutic doses may be necessary at intervals as life-threatening signs such as arrhythmias, convulsions, and deep coma recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

**INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.**

It has also been reported that ANTILIRIUM (physostigmine salicylate) may antagonize the CNS depressant effects of diazepam.

**CONTRAINDICATIONS**: Physostigmine salicylate injections should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents (decamethonium, succinylcholine).

**WARNING**: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions. An overdosage of ANTILIRIUM can cause a cholinergic crisis.

**PRECAUTIONS**: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is antagonist and antidote for physostigmine.

**ADMINISTRATION AND DOSAGE**: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur. Physostigmine salicylate is rapidly metabolized in the body.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: Ampuls, 2 ml. packed 12 per box.

OJ &F **O'NEAL, JONES & FELDMAN**
**ST. LOUIS, MISSOURI 63043**

1079

## ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA, effective

**From**—(Current or former address)

Street Address

City, State, Zip Code

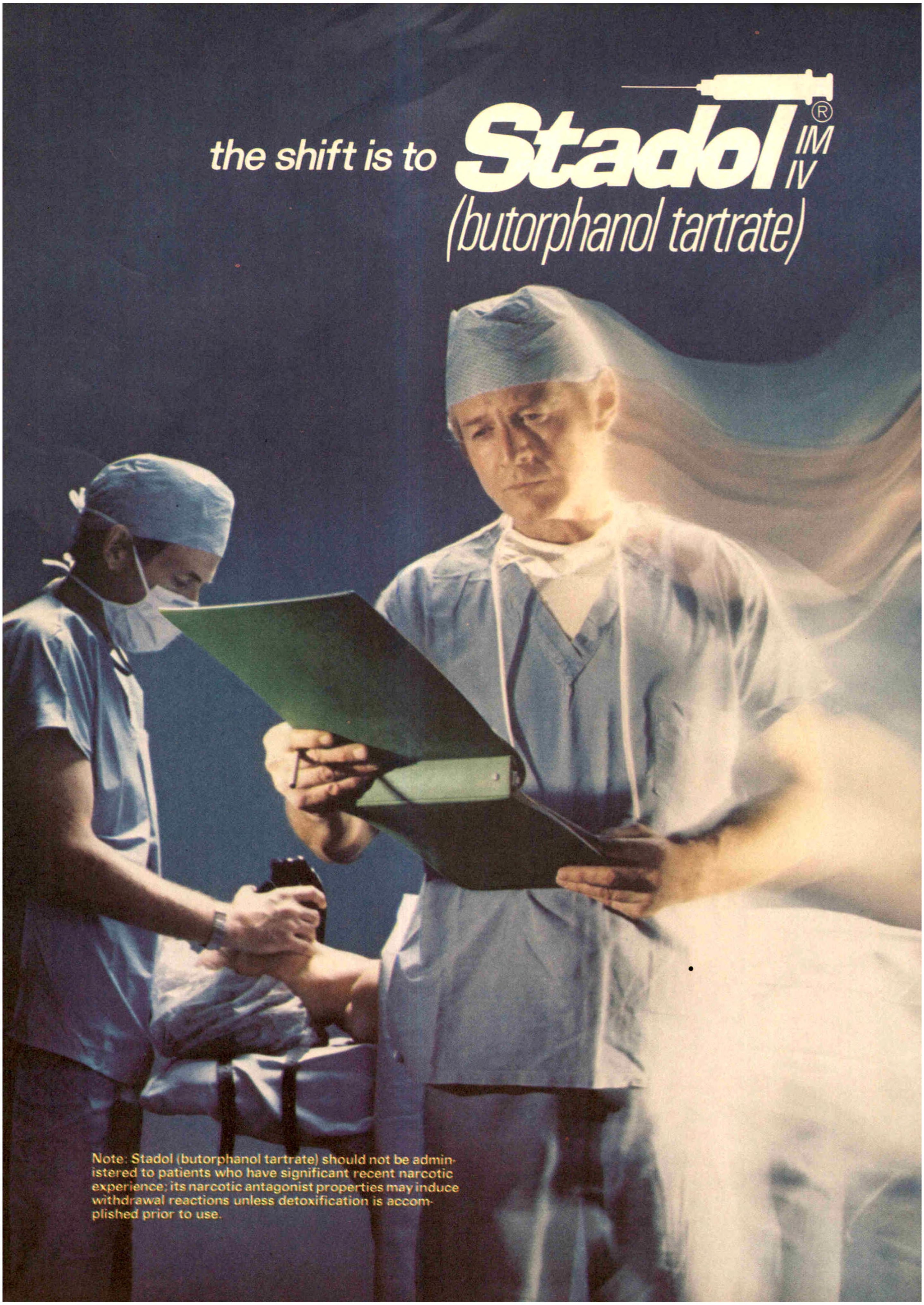
**Important: Show your name and address exactly as your Journal is now addressed.**

**To**—(New Address)

Street Address

City, State, Zip Code

Print Your Name


the shift is to Stadol® IM IV
(butorphanol tartrate)

Note: Stadol (butorphanol tartrate) should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.

*for pain management*

**preoperatively**
**intraoperatively**
**postoperatively**

*in surgery*

- **proven analgesic efficacy**—as a pre- and postoperative agent . . . for patients in labor . . . as the analgesic component of balanced anesthesia
- **fast acting**—onset of action within 10 minutes IM, very rapidly IV; peak analgesic activity within 30-60 minutes IM, more rapidly IV
- **limited respiratory depressant potential**—2 mg of Stadol produces a degree of respiratory depression similar to that of 10 mg of morphine or 70 mg of meperidine—unlike these agents, doubling the Stadol dose to 4 mg does not appreciably increase the magnitude of respiratory depression
- **favorable side effect profile**—low physical dependence liability, little nausea or vomiting, infrequent constipation
- **few CNS effects other than sedation**—the reported incidence of euphoria and hallucinations is less than 1%
- **nonscheduled**—not subject to regulations under the Federal Controlled Substances Act

**Stadol® IM IV**
(butorphanol tartrate)

*proven performance in the relief of moderate to severe pain*

**BRISTOL™**

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

Please see brief summary of prescribing information on the following page.

Copyright © 1980, Bristol Laboratories

**Brief Summary of Prescribing Information**
**STADOL® (butorphanol tartrate)**

For complete information, consult Official Package Circular.

(2) 12/10/79

**INDICATIONS AND USAGE**—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

**CONTRAINDICATIONS**—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

**WARNINGS—Patients Physically Dependent on Narcotics:** Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

**Drug Dependence:** Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

**Head Injury and Increased Intracranial Pressure:** Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

**Cardiovascular Effects:** Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

**PRECAUTIONS—Certain Respiratory Conditions:** Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

**Impaired Renal or Hepatic Function:** Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

**Biliary Surgery:** Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

**Usage as a Preoperative or Preanesthetic Medication:** Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

**Usage in Balanced Anesthesia:** The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

**Usage in Pregnancy:** The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

**Usage in Labor and Delivery:** Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

**Usage in Nursing Mothers:** The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

**Usage in Children:** Safety and efficacy in children below age 18 years have not been established.

**ADVERSE REACTIONS**—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

**CNS:** nervousness, unusual dreams, agitation, euphoria, hallucinations

**Autonomic:** flushing and warmth, dry mouth, sensitivity to cold

**Cardiovascular:** palpitation, increase or decrease of blood pressure

**Gastrointestinal:** vomiting

**Respiratory:** slowing of respiration, shallow breathing

**Dermatological:** rash or hives

**Eye:** diplopia or blurred vision

**OVERDOSAGE—Manifestations:** Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

**Treatment:** The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

**HOW SUPPLIED**—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

**NDC** 0015-5644-20—2 mg per ml, 2-ml vial
**NDC** 0015-5645-20—1 mg per ml, 1-ml vial
**NDC** 0015-5646-20—2 mg per ml, 1-ml vial
**NDC** 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
**NDC** 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

**BRISTOL™**

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

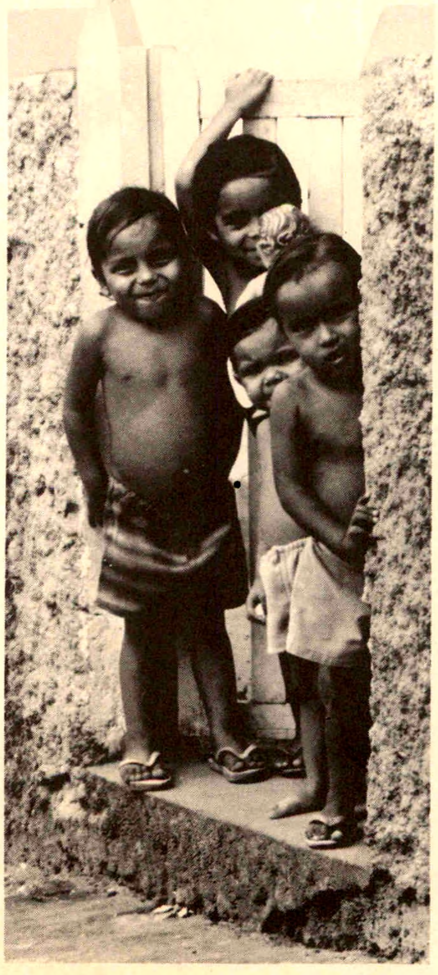
# Some doors are meant to be open...

Project HOPE is opening doors to children like these throughout the world. Since 1960 HOPE has sent teams of physicians, dentists, nurses and allied health personnel to share with developing nations their medical skills and knowledge.

Give to:

**PROJECT HOPE**

Department A
Washington, D.C. 20007



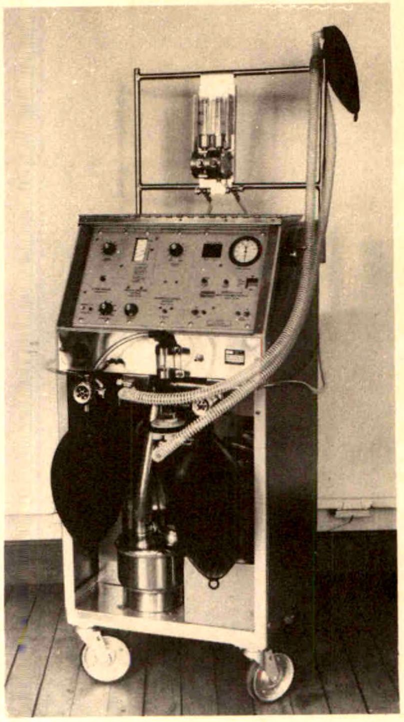
# EMERSON IMV Ventilator

## *Intermittent Mandatory Ventilation*

Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]



## VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of $CO_2$ rise, as noted by Kirby and associates.[1]

## VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

*Please request Form 3-IMV.*

**J. H. EMERSON COMPANY**
**CAMBRIDGE, MASSACHUSETTS 02140**

FAILURE TO USE THE NICHOLES 99 FILTER...

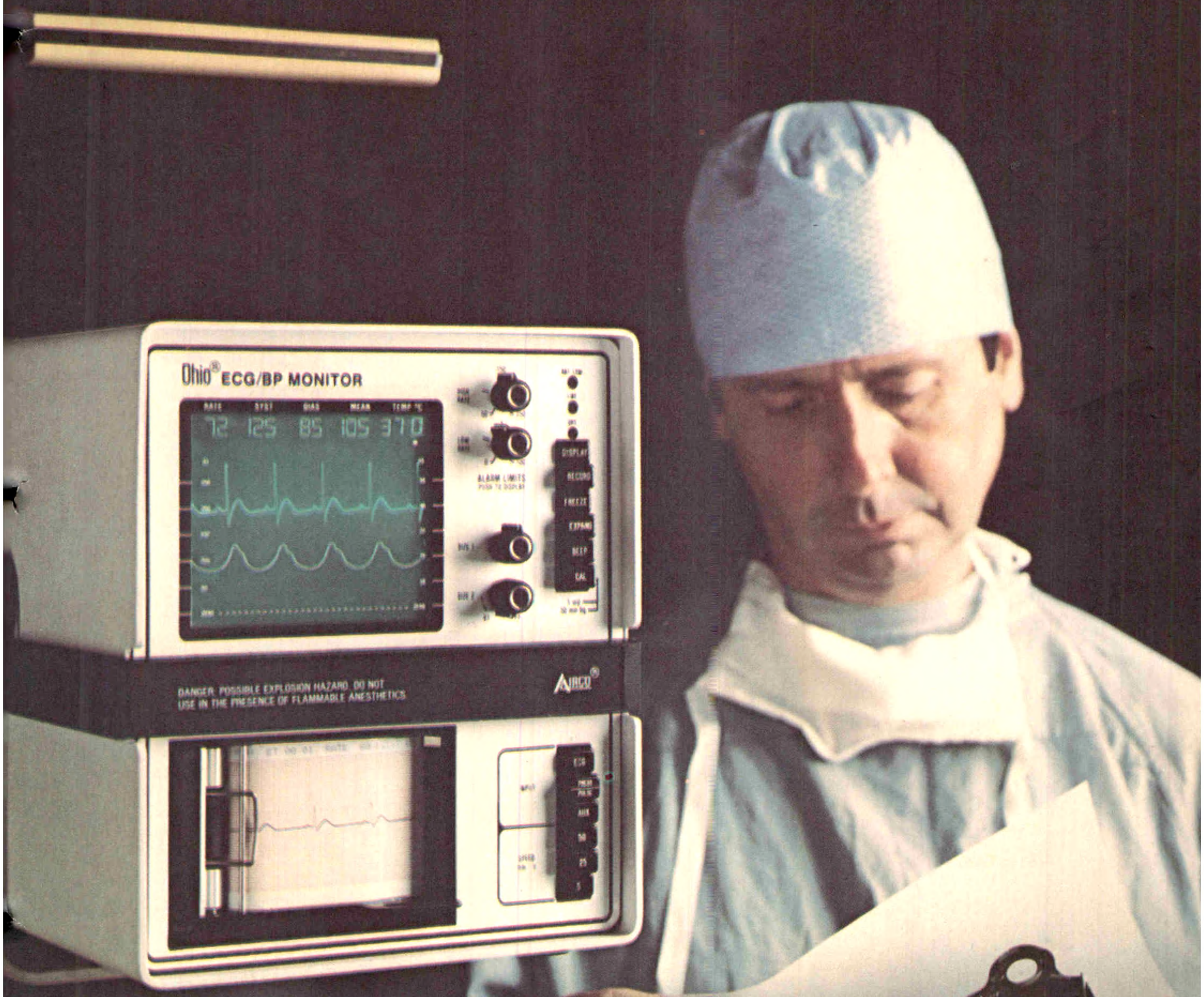
**NICHOLES-99**
VIRAL-BACTERIAL RETENTIVE FILTER

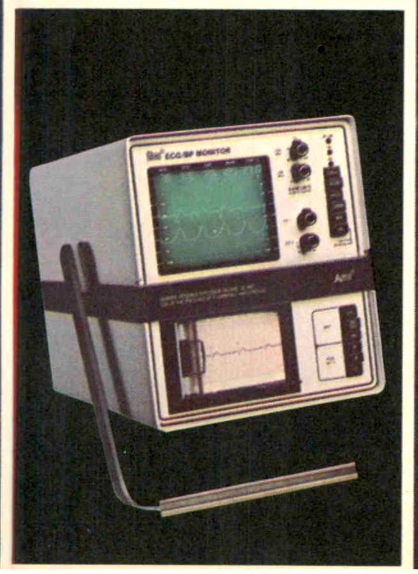
**NICHOLES II™**
THE 2nd GENERATION

Reprints of this ad available upon request, K & G Healthcare Industries, Inc. 5373 N.W. 36th Street,
Miami Springs, Florida 33166 (305) 871-3632

© K&G Healthcare, Inc. 1980

# Versatile Ohio Monitors give you a number of ways to view your patient.





In the O.R. where the types of surgery are so complex and varied, you need a monitoring system with the diverse capabilities of the Ohio® ECG/BP Monitor. Because it's versatile enough to give you a continuous reading on as many as five of your patient's vital signs.

Bright, sharp numeric readouts and dual-traces indicate your patient's ECG, body temperature, heart rate, blood pressure or peripheral pulse. Accurately and continually. What's more, the Ohio Monitor gives you the added flexibility of a waveform freeze and expand function for further, in-depth study.

Add an optional annotating recorder to your Ohio ECG/BP Monitor, and record both alphanumeric and waveform data permanently for more detailed analysis or inclusion in the patient's file

**All the right numbers. All the time.**

There are times when other monitors might distort or blackout altogether. But with the dual-trace Ohio ECG/BP Monitor, you keep your patient's status in view constantly. A special electrosurgical interference suppression system and other electronic safeguards ensure monitoring continuity.

The Ohio ECG/BP Monitor. It's compact, easy to use. Yet versatile enough to give you a clearer view of your patient, a number of ways.

**Ohio Medical Products**
3030 Airco Drive, P.O. Box 7550, Madison, Wisconsin 53707

A DIVISION OF AIRCO INC.

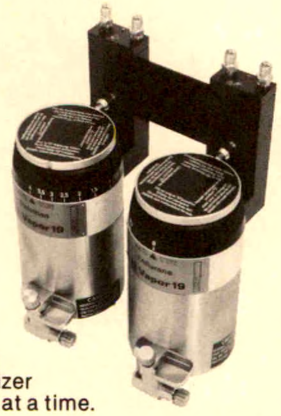
© 1979 Airco, Inc.

# NEW from NORTH AMERICAN DRÄGER

North American Drager is continually keeping in touch with the growing needs of the anesthesia profession. We are constantly improving our products for patient safety, our prime engineering and design criterion. These new products join the ever growing range of North American Drager Products of Anesthesia.

**DPM 2**
**(DRAGER PRESSURE MONITOR II)**

Our second generation of pressure monitors.
Four pressure monitors—minimum ventilation pressure, continuing pressure, high pressure and sub atmosphere pressure.

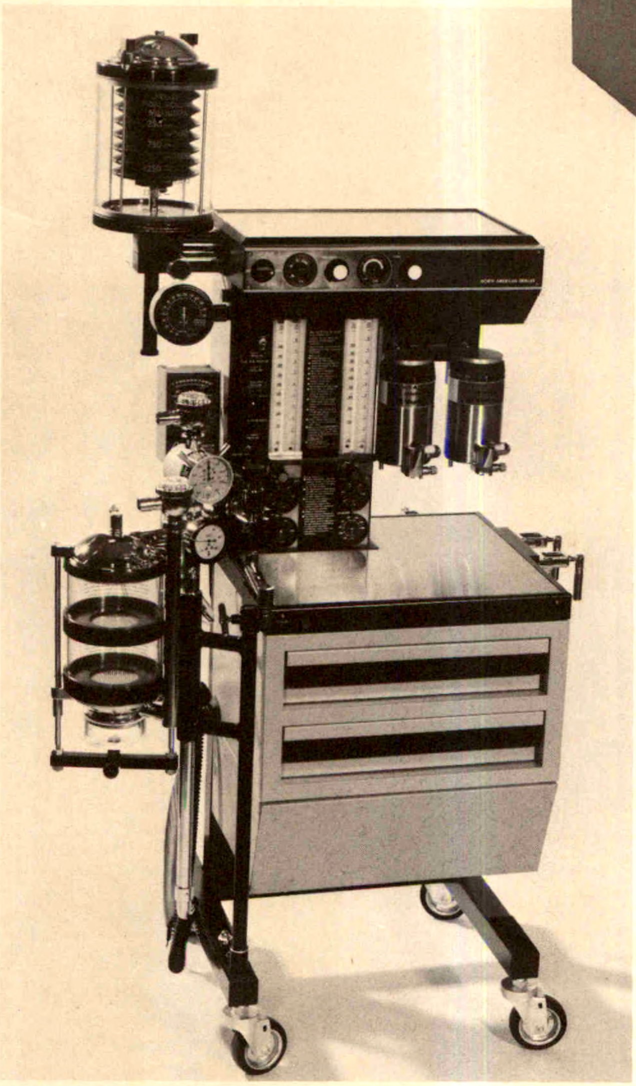


**VAPORIZER EXCLUSION SYSTEM**

A unique lock out system for insuring that only one vaporizer can be switched on at a time.

**PHILLIPS LARYNGOSCOPE BLADE**

Combines the features of the Miller Blade and the Jackson-Eversole Blade. Now in Two Sizes—Adult and Pediatric.



**NARKOMED 2 ANESTHESIA SYSTEM**

The newest member of the North American Drager family of Anesthesia Systems.
A complete anesthesia system consisting of an anesthesia dispensing system, ventilation system, patient monitoring system and a unique patient safety alarm system.

NORTH AMERICAN DRÄGER
*148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969*

NORTH AMERICAN DRÄGER
*148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969*

☐ Please send Anesthesia Accessories catalog

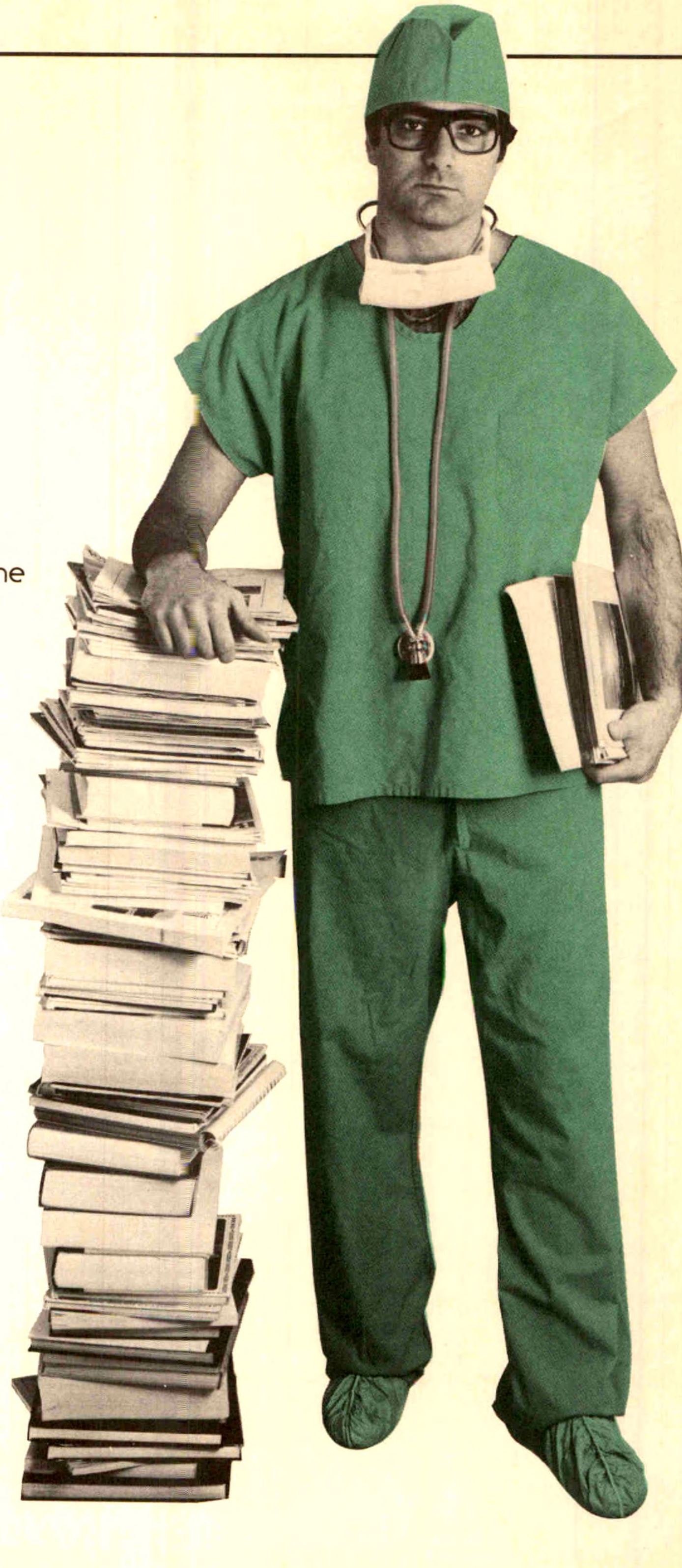
☐ Please have N.A.D. representative call

☐ Please include information on Anesthesia Machines

NAME ____________________
DEPARTMENT ____________________
HOSPITAL ____________________
ADDRESS ____________________
CITY ____________________ STATE ______ ZIP ______
TELEPHONE ____________________

# Halothane U.S.P.

## The "Familiar Territory" Anesthetic



**HALOTHANE—THE WORLD'S STANDARD**

- **Experience:** thousands of publications, millions of administrations.
- **Consistency:** no surprises in the OR or recovery room.
- **Cost:** one-seventh the cost of enflurane per administration.

**HALOCARBON—AN INDUSTRY LEADER**

- **Experience:** first manufacturer of fluorinated anesthetics in the U.S.
- **Consistency:** pioneered in the manufacture of the consistently purest anesthetic in the world.
- **Cost:** the lowest price schedule of any potent anesthetic.

**HALOCARBON**
LABORATORIES, INC.
82 Burlews Court
Hackensack, N.J. 07601
(201) 343-8703

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

## 55th CONGRESS to be held MARCH 8–12, 1981

## PEACHTREE PLAZA HOTEL, ATLANTA, GEORGIA

**CALL FOR PAPERS**

AUGUST 22, 1980 DEADLINE

If you would like to submit a paper for consideration by the Program Committee, please note the deadline for submitting title and 300-word abstract is August 22, 1980.

For official application form, please write or call:

E. Paul Didier, M.D., Chairman
Program Committee for 55th Congress
c/o Department of Anesthesiology
Mayo Clinic
200 First Street, SW
Rochester, Minnesota 55901

Telephone: (507) 286-8766

---

SCIENTIFIC EXHIBITS: Requests for applications for scientific exhibit space should be sent to: B. B. Sankey, M.D., International Anesthesia Research Society, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. (Please note the above deadline does not apply to scientific space applications which can be accepted, on a space availability basis, up to December 31, 1980.)

**MARK YOUR CALENDAR NOW—PLAN TO ATTEND THIS IMPORTANT CONTINUING MEDICAL EDUCATION ACTIVITY**

# EDITORIAL

# A Stressful Situation

FATAL febrile responses to anesthesia have been known since the turn of the century, but it was not until the seventh decade that the familial neuromuscular syndrome known as malignant hyperthermia (MH) was well described. Since most of the infrequent case reports involved drugs, particularly the potent inhalation anesthetics and muscle relaxants, MH was considered a relatively rare pharmacogenetic problem. Few anesthesiologists expected to see a case of MH. But as better techniques of diagnosis became available, i.e., in vitro muscle testing, it became apparent that susceptibility to MH (MHS) was neither rare nor uncommon. As additional information became available, inconsistent and atypical patterns of response in MHS patients were recognized, suggesting that MH could not be considered a pure, relatively rare problem with well described characteristics. Since the mechanisms and the nature of the problems are still poorly described and in many instances based on speculation, these inconsistencies have led to confusion about MH.

Several things have, however, become clear during the past two decades. First, MH is not always associated with a fulminant fever. Recognition of this important point along with the other inconsistencies led to considerable debate at the Second International Symposium on Malignant Hyperthermia concerning the appropriateness of the name.[1] However, the name was not changed because there was not enough information available to propose an acceptable substitute. Second, and more important, is the fact that most MHS patients can be anesthetized with the so-called contraindicated drugs without developing MH.[2, 3] Indeed, this is the rule rather than the exception. In addition, patients who have had documented MH reactions have successfully been subsequently anesthetized with the contraindicated drugs (S. Tan and J. A. Aldrete, presentation at Second International Symposium on Malignant Hyperthermia, Denver, Colorado, 1977 and references 3 and 4). This information suggests that factors other than drugs and inheritance are necessary for MH to develop. Furthermore, this information causes serious doubt as to the role of incomplete penetrance of the MH gene(s) as an important reason why susceptibility infrequently expresses itself. Third, cases of MH were recognized to be "induced" in the recovery and postoperative periods when obviously the major effects of anesthesia were no longer an important consideration. It has been my experience after reviewing more than 3000 episodes in MHS patients that more problems occur following anesthesia than occur during anesthesia. In fact, the patient may be safer in the operating room than in the recovery room or following discharge from the recovery room.

Obviously, a new and more expanded concept of MH has become necessary to accommodate these inconsistencies. Thus, the next step has been development of the concept that one of the other factors in MH is stress.[5] It has been known for many years that stress exacerbates neuromuscular diseases. Retrospective analysis of MH families suggests a stress-induced sudden death syndrome with MHS; this has been reinforced by studies implicating intrinsic cardiac problems with accompanying cardiac irregularities and potential fatal arrhythmias as an explanation for the sudden deaths.[6] Interestingly, fever is not a major component of these latter findings.

In this issue, Gronert, Thompson, and Onofrio (Anesth Analg 59:377–378, 1980) supply further information which strengthens the stress concept of MH. They have successfully identified by in vitro muscle testing an MHS patient, recognized an MH-like stress-induced reaction, and successfully treated the patient with dantrolene. The patient was *not* anesthetized, was *not* taking any medications, and was *not* hospitalized. One might argue that the MH reaction was not witnessed by the authors nor do they have good evidence of major biochemical abnormalities to substantiate their claim that the patient had MH. Certainly the clinical response was malignant hyperthermoid and the patient had a transient diabetic pattern, a biochemical abnormality consistent with a stress response. This report leaves only one conclusion: MHS when associated with stress caused a potentially fatal condition in the patient. The implications of this extend far beyond the scope of anesthesiology. Reports of the adverse effects of stress secondary to modern life styles on the general health of our population are voluminous. What is the impact of MHS on the stress problems in the general population? In view of the prevalence of MHS and increasing reports of sudden death with MHS, one can speculate with some assurance that it is a medical problem of considerable magnitude. The importance of this aspect of MHS should not be taken lightly.

It is interesting that dantrolene can abort a stress-induced MH-like syndrome such as occurred in the patient described by Gronert et al. Dantrolene is not considered a sympatholytic or adrenolytic agent. Did it reduce the muscle response without influencing the other parts of the stress response, especially the effects of stress on the cardiovascular system? Or did dantrolene have beneficial effects on the entire sympathoadrenal response? If the latter is true, why might this drug work as well or possibly better than sympatholytic drugs, as it does in the pig? Dantrolene will abort the MHS stress response, but will it protect against sudden death? Theoretically it should not, if the cardiac problems in MHS are intrinsic to the heart because dantrolene has minimal cardiovascular effects. It is hard to imagine that merely blocking skeletal muscle sarcoplasmic reticulum could abort a stress response, yet it does. Obviously, in the next decade we can look forward with excitement to developments of our understanding of MH, its diagnosis and treatment, and its effects on other disease processes.

Finally, as with porcine MH, human MH is a special variant of a more general stress syndrome. To assume that human and porcine MH are identical is folly because of species differences in their respective neuromuscular systems, in their biochemical mechanisms, and in their heat regulatory systems. Taking these species differences into account, it is equally fallacious to discount the similarities and the usefulness of the pig in developing insight into human MH. Gronert et al recognize these differences in their report.

A concept that takes into account all of these factors has evolved.[4] Malignant hyperthermia is an inherited neuromuscular problem(s) with its own characteristics which express themselves independent of stress and drugs and which under adverse conditions may give rise to nonhyperthermic metabolic problems. As with all patients, stress results in increased sympathoadrenal activity characterized by tachycardia, hypertension, increased metabolic activity, venoconstriction, and fever. In the MHS patient stress may or may not enhance the neuromuscular problems. When both are present the clinical picture is that seen in the patient of Gronert et al. The maximum effect of both is a potentially dangerous situation. Drugs may affect either or both of these components and the outcome depends upon the type of drug, the degree of the neuromuscular problem, and the amount of stress at the time the drugs are administered. The potent inhalation anesthetics and/or succinylcholine may make this condition worse. Again, the clinical picture during anesthesia depends upon the conditions existing in the patient at the time anesthetics are given. The more severe the underlying neuromuscular condition and the greater the stress, the more profound the MH reaction will be during anesthesia. When all are at their maximum, typical fulminant MH results. Thus, a spectrum of responses can be seen.

Daniel W. Wingard, MD
*Department of Anesthesiology*
*University of Nebraska College*
*of Medicine*
*Omaha, Nebraska 68105*

## REFERENCES

1. Kalow W: Concluding remarks, in Malignant Hyperthermia. Edited by JA Aldrete and BA Britt. New York, Grune & Stratton, 1978, p 553
2. Britt BA, Kalow W: Malignant hyperthermia: a statistical review. Can Anaesth Soc J 17:293, 1970
3. Halsall PJ, Cain PA, Ellis FR: Retrospective analysis of anaesthetics received by patients before susceptibility of malignant hyperpyrexia was recognized. Br J Anaesth 51:949, 1979
4. Wingard DW: Malignant hyperthermia: familial stress syndrome, in Inherited Diseases and Anaesthesia. Edited by FR Ellis. Amsterdam Elsevier, in press 1980
5. Wingard DW: Malignant hyperthermia—acute stress syndrome of man, in Malignant Hyperthermia, Current Concepts. Edited by EO Henschel. New York, Appleton-Century-Crofts, 1977, p 79
6. Huckell VF, Staniloff HM, McLaughlin PR, et al: Cardiovascular manifestations of normothermic malignant hyperthermia, in Malignant Hyperthermia. Edited by JA Aldrete and BA Britt. New York, Grune & Stratton, 1978, p 373

ANESTH ANALG
59:323-326, 1980

# Pulmonary and Systemic Vascular Responses to Nitrous Oxide in Patients with Mitral Stenosis and Pulmonary Hypertension

**John C. Hilgenberg, MD,* Richard L. McCammon, MD,* and Robert K. Stoelting, MD†**

---

HILGENBERG, J. C., MCCAMMON, R. L., AND STOELTING, R. K.: Pulmonary and systemic responses to nitrous oxide in patients with mitral stenosis and pulmonary hypertension. Anesth Analg 59:323–326, 1980.

Pulmonary and systemic circulatory responses to inhalation of 50% nitrous oxide were studied in 11 patients with pulmonary hypertension prior to elective mitral valve replacement. All patients were premedicated with intramuscular morphine and scopolamine. Compared with awake control measurements while breathing 50% oxygen in nitrogen, heart rate, cardiac index, systemic and pulmonary vascular pressures, systemic vascular resistance, and systemic and pulmonary heart rate, systolic blood pressure products remained unchanged after administration of 50% nitrous oxide for 10 minutes. The only significant change was an increase in pulmonary vascular resistance from 159 ± 18 dynes·sec·cm$^{-5}$ before nitrous oxide inhalation to 213 ± 27 dynes·sec·cm$^{-5}$ during nitrous oxide inhalation ($p < 0.05$). We conclude that nitrous oxide increases pulmonary vascular resistance in patients with preexisting pulmonary hypertension; however, this increase is not associated with alterations in other measured or calculated hemodynamic variables and is probably not of sufficient magnitude to recommend avoiding nitrous oxide in these patients.

**Key Words:** ANESTHETICS, Gases: nitrous oxide; LUNG: vascular resistance.

---

THE INHALATION of nitrous oxide following morphine administration in patients with coronary artery disease significantly increases mean pulmonary artery pressure and pulmonary vascular resistance while decreasing mean arterial pressure and cardiac index.[1] Increased pulmonary vascular resistance produced by nitrous oxide might be particularly undesirable in patients with preexisting pulmonary hypertension and right ventricular disease or right-to-left intracardiac shunts. Based on this concern the use of nitrous oxide in these types of patients has been questioned.[1] Nevertheless, measurements of the effects of nitrous oxide on the pulmonary circulation in patients with preexisting pulmonary hypertension are limited to the description of a single patient with mitral valve disease who received nitrous oxide after morphine, 1 mg/kg IV.[1] Data in a larger series of patients with pulmonary hypertension and receiving nitrous oxide in the absence of other drugs are necessary to resolve the question of the safety or hazard of nitrous oxide administration in such patients. Therefore, we studied the pulmonary and systemic vascular effects of nitrous oxide in 11 patients with pulmonary hypertension[2] prior to anesthesia for elective mitral valve replacement.

---

* Assistant Professor.

† Professor and Chairman.

Received from the Department of Anesthesia, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46223. Accepted for publication January 12, 1980.

Reprint requests to Dr. Hilgenberg.

## Method

Eleven patients with valvular heart disease (49 ± 2 years, 67 ± 4 kg, mean ± SEM) were studied before induction of anesthesia for elective mitral valve replacement. Preoperative mean pulmonary artery pressure was greater than 20 torr in all patients. None had angiographic evidence of coronary artery disease. Digitalis preparations had been discontinued for at least 48 hours. Two patients had atrial fibrillation. Morphine (6 to 15 mg) and scopolamine (0.4 to 0.6 mg) were administered intramuscularly 60 to 90 minutes before the patients were studied.

Peripheral intravenous cannulae were placed for fluid and drug infusion. Radial arterial cannulae were inserted for measurement of arterial blood pressure and blood gas sampling. A triple lumen flow-directed thermodilution catheter was advanced through the right internal jugular vein into a pulmonary artery for recording of pulmonary artery pressure (PAP), pulmonary artery occluded pressure ($PA_O$), and mean right atrial pressure (RAP), as well as for measurement of cardiac output (CO). Heart rate (HR) was calculated from the electrocardiogram. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) as $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ were calculated as follows: $\text{SVR} = \text{MAP} - \text{RAP} \times 80 \div \text{CO}$ and $\text{PVR} = \text{PAP} - PA_O \times 80 \div \text{CO}$. Cardiac index (CI) was calculated by dividing CO by body surface area and stroke index (SI) by dividing CI by HR. The rate-pressure product was determined by multiplication of heart rate by the systemic or pulmonary artery systolic pressure.

Awake control measurements were obtained while patients were breathing 50% $O_2$ in nitrogen by mask for 10 minutes. Following control measurements the inspired gases were changed to 50% nitrous oxide in oxygen (6 L/min $N_2O$: 6 L/min $O_2$). All measurements were repeated and arterial blood gas tensions and pH were determined after 10 minutes of nitrous oxide inhalation. Drugs were not administered and colloid was not infused during the period of data collection. Ventilation was spontaneous during the entire study period. All measurements were made at end-expiration. Data were analyzed using Student's *t*-test for paired data and $p < 0.05$ was considered statistically significant.

**TABLE 1**

**Hemodynamic Changes during Inhalation of 50% Nitrous Oxide by Patients with Pulmonary Hypertension (mean ± SEM)**

| | Control | Nitrous oxide (50% for 10 min) |
|---|---|---|
| Heart rate (beats/min) | 85.6 ± 5.4 | 82.5 ± 6.1 |
| Cardiac index ($L/min/m^2$) | 2.74 ± 0.15 | 2.50 ± 0.18 |
| Stroke index ($ml/min/m^2$) | 32.9 ± 2.5 | 31.4 ± 2.8 |
| Systemic arterial pressures (torr) | | |
| Systolic | 129.5 ± 6.1 | 126.9 ± 6.4 |
| Diastolic | 74.4 ± 2.4 | 75.8 ± 3.0 |
| Mean | 92.4 ± 3.1 | 92.5 ± 3.8 |
| Pulmonary arterial pressures (torr) | | |
| Systolic | 51.7 ± 4.8 | 52.3 ± 5.4 |
| Diastolic | 27.3 ± 2.6 | 31.4 ± 4.4 |
| Mean | 35.7 ± 3.3 | 38.3 ± 4.6 |
| Occluded | 26.7 ± 2.9 | 26.2 ± 3.0 |
| Mean right atrial pressure (torr) | 11.0 ± 1.9 | 15.6 ± 3.5 |
| Systemic vascular resistance ($\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$) | 1,451 ± 115 | 1,551 ± 124 |
| Pulmonary vascular resistance ($\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$) | 159 ± 18 | 213 ± 27* |
| Heart rate × systolic arterial pressure | 11,175 ± 916 | 10,654 ± 1192 |
| Heart rate × pulmonary arterial pressure | 4,419 ± 477 | 4,466 ± 653 |

* Significant ($p < 0.05$) difference between control and value obtained during $N_2O$ administration.

## Results

Data are summarized in Table 1. Compared with awake measurements while breathing 50% oxygen in nitrogen, the inhalation of 50% nitrous oxide in oxygen for 10 minutes resulted in no significant change in any measured hemodynamic parameter. Changes in RAP and CI approached but did not achieve statistical significance. PVR increased significantly ($p < 0.05$) when nitrous oxide was administered, while SVR did not change. Individual changes in PVR and PAP are depicted in Figs 1 and 2, respectively.

Arterial blood gas tensions, pH, and temperature data at the conclusion of the nitrous-oxide study are summarized in Table 2.

## Discussion

The effect of nitrous oxide on the systemic circulation has been studied alone,[3] in combination with inhalation anesthetic agents,[4] and after intravenous narcotic administration.[1, 5] When administered to healthy volunteers alone or in combination with inhalation anesthetics, nitrous oxide causes alpha-adrenergic stimulation and peripheral vasoconstriction. Significant myocardial depression is apparent when nitrous oxide is administered alone[3] or with intravenous narcotics.[1, 5]

The effect of nitrous oxide on the pulmonary circulation has not been as extensively investigated. Price et al[6] found no significant change in PAP or PVR in healthy patients during inhalation of either halothane-oxygen or halothane-nitrous oxide-oxygen. The addition of nitrous oxide to halothane-oxygen

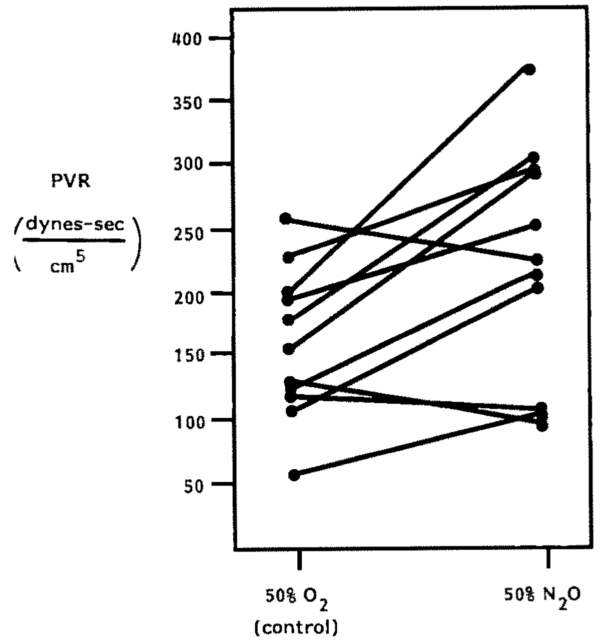


FIG 1. Individual pulmonary vascular resistance measurements (PVR) as determined in 11 patients before (control) and after 10 minutes of 50% $N_2O$ inhalation.

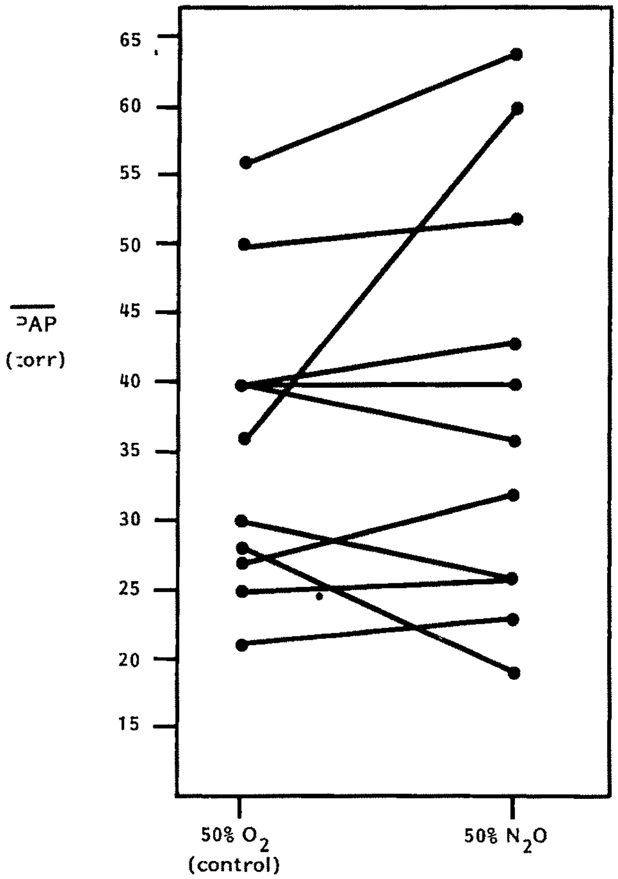


FIG 2. Individual mean pulmonary artery pressure measurements ($\overline{PAP}$) as determined in 11 patients before (control) and after 10 minutes of 50% $N_2O$ inhalation.

**TABLE 2**

**Blood Gas, pH, and Temperature Data after Breathing 50% Nitrogen in Oxygen and 50% Nitrous Oxide in Oxygen for 10 Minutes (mean ± SEM)**

| | 50% $N_2$ | 50% $N_2O$ |
|---|---|---|
| $Pa_{O_2}$ (torr) | 162 ± 14 | 176 ± 18 |
| $Pa_{CO_2}$ (torr) | 38.2 ± 2.1 | 38.9 ± 1.4 |
| pH | 7.42 ± 0.02 | 7.39 ± 0.01 |
| Temperature ( C) | | 36.6 ± 0.1 |

anesthesia in patients with aortic and/or mitral valvular heart disease resulted in no significant change in either $\overline{PAP}$ or PVR.[4] Lappas et al,[1] however, found that the addition of 50% nitrous oxide following morphine administration to patients during coronary artery surgery resulted in a small but significant increase in $\overline{PAP}$ and PVR. A subsequent study by the same authors again demonstrated similar changes in the pulmonary circulation during nitrous oxide-halothane anesthesia which were reversed by the administration of the ganglionic blocker, pentolinium.[7] Presumably nitrous oxide resulted in alpha-adrenergic stimulation which was reversed by pentolinium. Phentolamine, an alpha-adrenergic blocker, also reverses pulmonary vasoconstriction induced by nitrous oxide.[1] The discrepancy between earlier and more recent data may be explained in part by differences in study conditions and autonomic nervous system tone at the time of data collection, i.e. surgical stimulation, cardiovascular recovery with time, or background anesthetic.

Drug-induced pulmonary vasoconstriction can be inferred if the $\overline{PAP}$ increases in the presence of the following conditions: (1) a constant or decreased CO; (2) a constant left atrial pressure; (3) an unchanged extravascular pressure within the lungs and thorax; and (4) constant HR, systemic arterial pressure, and pulmonary blood volume.[8] Cardiac output, PAP, mean arterial pressure (MAP), HR, and $PA_O$ did not change during nitrous oxide administration in our subjects. The extravascular pressure in the lungs and thorax are assumed to have remained constant since there was no significant change in airway pressure or ventilatory pattern during spontaneous ventilation and measurements were made at end-expiration. It can be inferred that no significant change in pulmonary blood volume occurred during data collection since no blood or colloid was being infused nor was redistribution between systemic and pulmonary vasculatures likely since neither MAP nor SVR changed. Furthermore, blood viscosity, an important determinant of PVR, was unlikely to have changed during the course of data collection. Thus, our data demonstrating increased PVR during nitrous oxide administration are consistent with a drug-induced pulmonary vasoconstriction.

Our results are in agreement with previous studies demonstrating a significant change in pulmonary vascular hemodynamics during nitrous oxide inhalation.[1, 7] Our patient population is unique in that all patients had moderate pulmonary hypertension as evidenced by the mean pulmonary artery pressure of 35.7 torr. Furthermore, background anesthesia and surgical stimulation were not present. Alterations in autonomic nervous system tone by general anesthesia or surgical stimulation may significantly alter the response to sympathetic stimulation and thus confuse the interpretation of data obtained from drug administration under these conditions.

The clinical significance of the ability of nitrous oxide to induce pulmonary vasoconstriction has not been fully elucidated. Lappas, et al[1] observed a significant increase in the right ventricular rate-pressure product when nitrous oxide was inhaled following morphine administration during controlled ventilation in patients without pulmonary hypertension. Our results in patients with pulmonary hypertension spontaneously breathing nitrous oxide alone failed to demonstrate a significant change in right ventricular rate-pressure product. This was because neither pulmonary artery systolic pressure nor HR significantly changed. Thus, in our patients with mitral stenosis, one index of right ventricular myocardial oxygen consumption was not elevated.

In summary, the pulmonary and systemic vascular hemodynamic responses to the inhalation of nitrous oxide during spontaneous ventilation in patients with mitral stenosis and pulmonary hypertension revealed no significant change in any measured variable. Calculated PVR demonstrated pulmonary vasoconstriction. No detrimental effect on right ventricular myocardial oxygen resuirements was detected. Although the interaction between anesthetic agents and nitrous oxide inhalation may result in a small increase in PVR, we conclude that the effect of nitrous oxide on pulmonary vascular hemodynamics is not sufficient to recommend avoidance of nitrous oxide in patients with moderate pulmonary hypertension.

## REFERENCES

1. Lappas, DG, Buckley MJ, Laver MB, et al: Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary-artery surgery. Anesthesiology 43:61–69, 1975
2. Hurst JW: Pulmonary hypertension, in The Heart, Arteries, and Veins. Fourth edition. Edited by JW Hurst, RB Logue, RC Schlant, et al. New York, McGraw-Hill Book Co, 1978, pp 1456–1458
3. Eisele JH, Smith NT: Cardiovascular effects of 40 per cent nitrous oxide in man. Anesth Analg 51:956–963, 1972
4. Stoelting RK, Reis RR, Longnecker DE: Hemodynamic responses to nitrous oxide-halothane and halothane in patients with valvular heart disease. Anesthesiology 37:430–435, 1972
5. Stoelting RK, Gibbs PS, Creasser CW, et al: Hemodynamic and ventilatory responses to fentanyl, fentanyl-droperidol, and nitrous oxide in patients with acquired valvular heart disease. Anesthesiology 42:319–324, 1975
6. Price HL, Cooperman LH, Warden JC, et al: Pulmonary hemodynamics during general anesthesia in man. Anesthesiology 30: 629–636, 1967
7. Fahmy NR, Selwyn AS, Patel D, et al: Pulmonary vasomotor tone during general anesthesia and deliberate hypotension in man. Anesthesiology 45:3–13, 1976
8. Fritts HW Jr, Harris P, Clauss RH, et al: The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. J Clin Invest 37:99–110, 1958

ANESTH ANALG
59:327-334, 1980

# In Vivo Changes in Canine Ventricular Cardiac Conduction during Halothane Anesthesia

**Lawrence A. Turner, MD,* Edward J. Zuperku PhD,† Robert V. Purtock, PhD, and John P. Kampine, MD, PhD‡**

---

TURNER, L. A., ZUPERKU, E. J., PURTOCK, R. V., AND KAMPINE, J. P.: In vivo changes in canine ventricular cardiac conduction during halothane anesthesia. Anesth Analg 59:327–334, 1980.

Changes in the ventricular conduction system associated with halothane anesthesia were investigated by direct methods of His bundle recording, pacing, and premature stimulation in a canine model. In eight animals a change from 1.5% to 2.4% halothane concentrations was associated with significant prolongation of epicardial activation times by an average of 2.4 and 2.9 msec during atrial and His bundle paced rhythms, respectively. Ventricular functional refractory periods decreased significantly by an average of 7.3 msec, the effective refractory period of the ventricular conduction system did not change, and epicardial conduction delays at the effective refractory period decreased. In six other animals the addition of 1.5% halothane to basal thiopental anesthesia was not associated with prolongation of epicardial activation times or decreased ventricular functional refractory periods. However, the effective refractory period of the ventricular conduction system significantly decreased by an average of 9.1 msec, and epicardial conduction delays at the effective refractory period significantly increased by an average of 9.6 msec. A change in halothane concentrations from 1.5% to 2.4% is associated with depression of ventricular conduction and shortened duration of refractory periods in the ventricular conduction system in vivo in a manner consistent with the reported actions of halothane on Purkinje fibers in vitro.

**Key Words:** ANESTHETICS, Volatile: halothane; HEART: conduction.

---

CARDIAC arrhythmias are thought to result from disturbances of automaticity or conduction, or both.[1] The possible contribution of conduction disturbances to the genesis of ventricular arrhythmias in vivo during general anesthesia remains largely unknown. Disturbances characterized by diminished conduction velocity or "depressed" conduction and shortened refractory period durations may in theory facilitate the occurrence of arrhythmias by a reentrant mechanism.[2]

There is electrophysiologic evidence that the anesthetic halothane may depress conduction and shorten refractory period duration in ventricular tissues. Hauswirth[3] found that conduction times along Purkinje fibers were prolonged and the action potential and refractory period durations of Purkinje fibers were shortened by the addition of 2% halothane to a tissue bath. Changes in ventricular conduction associated with halothane anesthesia in vivo have been

---

* Assistant Professor, Department of Anesthesiology, The Medical College of Wisconsin.

† Associate Professor, Department of Anesthesiology, The Medical College of Wisconsin; Assistant Clinical Professor, Department of Biomedical Engineering, Marquette University, Milwaukee, Wisconsin; Biomedical Engineer, Research Service, VA Medical Center, Wood, Wisconsin.

‡ Professor, Departments of Anesthesiology and Physiology, The Medical College of Wisconsin; Associate Chief of Staff for Research and Development, Research Service, VA Medical Center, Wood, Wisconsin.

Supported by a grant from the National Heart, Blood and Lung Institute (HL 16511) and by the Medical Research Service of the Veterans Administration.

Received from the Department of Anesthesiology, The Medical College of Wisconsin, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226. Accepted for publication January 14, 1980.

Reprint requests to Dr. Turner.

demonstrated in several canine studies. Atlee et al[4, 5] have reported that there is dose-related prolongation by halothane of the interval between onset of the catheter-recorded wave form of the bundle of His and the earliest onset of ventricular muscle activity (H-V interval). However, Morrow et al[6] did not find prolongation of H-V intervals when halothane was given to animals initially anesthetized with pentobarbital.

The purpose of the present study was to examine changes occurring in the ventricular conduction system associated with halothane anesthesia in the presence and absence of basal barbiturate anesthesia. It was felt that the different changes in H-V intervals previously reported deserve further study. In addition, we studied changes in refractoriness in the ventricular conduction system at two levels of halothane anesthesia and with the addition of halothane to basal barbiturate anesthesia. The invasive methods utilized were adapted from those developed by Hoffman and co-workers[7] for direct measurement of conduction intervals between the His bundle and epicardium. A His bundle extrastimulus technique was employed to assess changes occurring in the refractory periods of the ventricular conduction system.[8]

## Methods and Materials

In 14 adult mongrel dogs anesthesia was induced with thiopental. The animals were intubated endotracheally without muscle relaxants and mechanically ventilated with oxygen. In group I (eight animals) anesthesia was maintained with halothane following an average induction dose of 17 mg/kg of thiopental. Fixed inspired concentration settings (Dräger vaporizer) and flow rates were used at each halothane concentration and at least ½ hour was allowed for equilibration following a change in concentration before parameters were determined. End-tidal concentrations were sampled in three animals on five occasions at each level. The average halothane concentrations (Beckman LB-2 analyzer) were 1.5% (range 1.4–1.6%) and 2.4% (range 2.3–2.5%) at the low and high levels, respectively. In group II (six animals) basal anesthesia was maintained by incremental injections of thiopental. The mean total dosage was 116 mg/kg over the 6 to 10 hours of the experiments. Halothane was added to basal thiopental anesthesia intermittently by the same methods, giving an average end-tidal concentration of 1.5% as above. The sequence of different anesthetic conditions within each group was randomized to limit the possible influence of time-dependent changes.

The experimental preparation is shown schematically in Fig 1. Bipolar epicardial electrograms were obtained from the right ventricular apex, left apex, and left base following a right thoracotomy. A quadripolar pacing and recording electrode was sutured directly over the bundle of His during short periods of venous inflow occlusion averaging 3.3 minutes. Animals having persisting ST-T wave changes, altered QRS configuration in either of two limb leads or changed sequence of activation at the epicardial recording sites were excluded from further study. His bundle activity was usually obtainable from any combination of the four poles of the electrode. A band pass filter set between 50 and 500 Hz was used to obtain the best possible wave form. Simultaneous electrogram tracings, limb lead I, and aortic pressure were recorded at speeds of 20 cm/sec on a Honeywell Visicorder system. A superimposed grid pattern at 10.0 ± 0.1-msec intervals was used for manual interval measurements.

His bundle pacing was performed by a coupled 2-channel Medtronic model 5837 pacemaker and associated logic device. The pacemaker provided pairs of 2-msec square wave constant current pacing pulses at

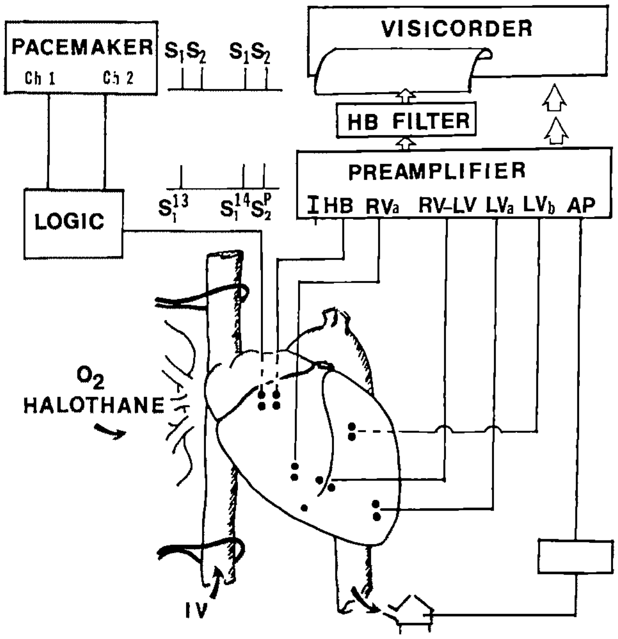


FIG 1. Diagram of the experimental preparation. $S_1^{13}$ and $S_1^{14}$ are the last two of a series of 14 His bundle pacing stimuli, and $S_2^P$ is the following premature test stimulus. Bipolar recording sites located as illustrated are abbreviated as follows: HB, His bundle; $RV_a$, right ventricular apex; RV-LV, one pole each side of the apex; $LV_a$, left ventricular apex; and $LV_b$, left ventricular base. All bipolar electrograms, limb lead I, and aortic pressure (AP) were recorded simultaneously.

controlled rate, amplitude, and coupling relationship. Diastolic thresholds were 3.4 and 3.7 ma in groups I and II, respectively, and pacing parameters were maintained constant at about twice the initial diastolic threshold throughout each experiment. Capture of the His bundle was considered valid if the QRS configuration in two limb leads and activation sequence at the epicardial recording sites remained the same at all pacing rates as that found during conducted atrial rhythms.

Arterial blood was sampled, gas tensions measured (Radiometer), and ventilation adjusted or bicarbonate given as required to maintain $Pa_{CO_2}$ between 33 and 46 torr, and pH between 7.33 and 7.48. Core temperature was monitored and maintained between 37.5–39 C. Lactated Ringer's solution (15 to 20 ml/kg/hr) was given to support the blood pressure and decrease spontaneous heart rate. Average systolic and diastolic blood pressures decreased from 94/68 to 76/50 torr on change to the high halothane level in group I and from 121/89 to 82/58 torr on addition of halothane to basal thiopental anesthesia in group II. Similarly, mean pH decreased from 7.41 to 7.37 in group I, and did not change from 7.39 in group II.

A standard protocol of interval measurements was followed under each set of anesthetic conditions. Conduction of regular (nonpremature) beats through the ventricular conduction system was assessed by measuring activation times at each epicardial recording site relative to the onset of His bundle activity. Epicardial activation times (EAT), defined as the interval between the onset of the His bundle wave form and the onset of each of the three epicardial deflections, were measured initially during atrial rhythms. His bundle pacing was then performed at rates of 125, 150, and 175 beats per minute, and similar EAT measurements were made from the onset of the pacing artifact which obscured the His bundle wave form during pacing.

An extrastimulus technique was used at each pacing rate to assess the refractory periods of the ventricular conduction system and determine the conduction delays resulting from premature stimulation of the bundle of His. As illustrated in the example tracings of Fig 2, a premature His bundle test stimulus ($S_2^P$) was used to scan the diastolic interval following every 14th His bundle pacing stimulus ($S_1^{14}$). The coupling interval of the test stimulus was progressively reduced after each series of 14 regular pacing stimuli by steps of 5 to 10 msec until the premature stimulus would no longer propagate to the ventricles. The effective refractory period (ERP) was measured directly as the interval between the last of a series of paced beats ($S_1^{14}$) and the earliest premature His bundle stimulus ($S_2^P$) that was able to propagate through the ventricular conduction system to capture the ventricles. As shown in Fig 2, as the coupling interval was reduced the premature complexes became aberrant and activation at the epicardial recording sites was progressively delayed. Conduction delay to each recording site was quantitated by determining the difference in epicardial activation times between the last pacing stimulus and the following premature test stimulus ($EAT_2^P - EAT_1^{14}$) as a function of the prematurity.

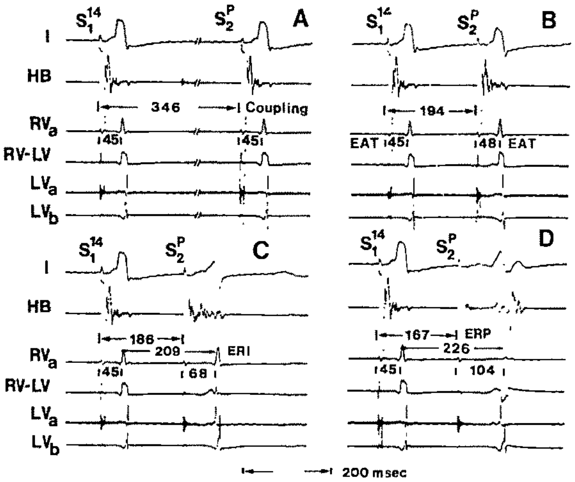


FIG 2. Electrogram tracings illustrating the methods of interval measurements for the RV$_a$ site in one animal (pacing rate 125 beats per minute, 1.5% halothane). All intervals are in milliseconds. A to D show pairs of complexes resulting from the last of a series of pacing stimuli ($S_1^{14}$) and the following premature test stimulus ($S_2^P$) at example coupling intervals ($S_1^{14}$ to $S_2^P$ interval (A)) decreasing from 346 to 167 msec. The intervals below the RV$_a$ tracing indicate the epicardial activation times (EAT (B)) for each complex. C illustrates the measurement of an epicardial response interval (ERI), the interval between epicardial deflections in response to $S_1^{14}$ and $S_2^P$, at a coupling interval of 186 msec. D shows conduction at the effective refractory period (ERP), defined as the interval between $S_1^{14}$ and the earliest propagating $S_2^P$ stimulus. The difference in EAT between the $S_2^P$ and $S_1^{14}$ complexes ($EAT_2^P - EAT_1^{14}$) at the ERP was derived and defined as the epicardial conduction delay at the effective refractory period ($CD_{ERP}$), in this case 104 − 45 = 59 msec.

Fig 3 illustrates data obtained at one recording site and one pacing rate during a complete coupling scan. The abscissas of both graphs are the coupling intervals or degree of prematurity. The ordinate to the right shows the difference in EAT between the $S_2^P$ and $S_1^{14}$ complexes. This epicardial conduction delay associated with prematurity was analyzed at the coupling interval giving the effective refractory period and is designated $CD_{ERP}$ in Fig 3. The ordinate to the left represents the interval between epicardial deflections of the $S_1^{14}$ and $S_2^P$ complexes. These intervals, designated the epicardial response intervals (ERI) in Figs 2

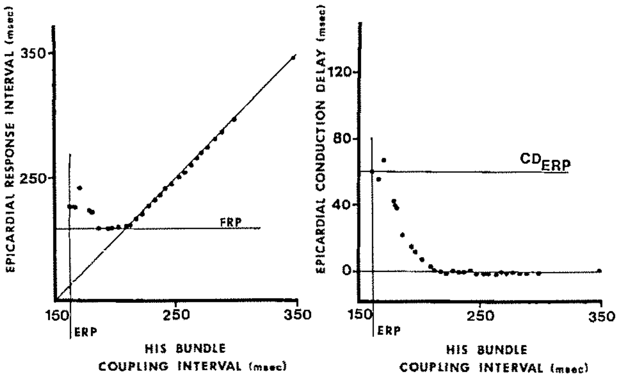


FIG 3. Complete plot of interval data obtained for the RV$_a$ site at all coupling intervals from the same animal under the same conditions as in Fig 2. The abscissas are the coupling intervals, or the degree of prematurity. The ordinate to the right is the difference in EAT between the $S_2^2$ and $S_1^{14}$ complexes, or the epicardial conduction delay. CD$_{ERP}$ indicates the epicardial conduction delay at the effective refractory period (ERP). The ordinate to the left represents the epicardial response intervals. The minimum epicardial response interval was measured and defined as the functional refractory period (FRP) for the conduction pathway to each recording site.

**TABLE 1**

**Mean Epicardial Activation Times at Two Levels of Halothane Anesthesia**

| Group I (N = 8) Epicardial recording site‡ | Atrial rhythm: Vol % halothane† 1.5% | Atrial rhythm: Vol % halothane† 2.4% | Atrial rhythm: Paired mean change ± SE | His bundle paced rhythm: Vol % Halothane† 1.5% | His bundle paced rhythm: Vol % Halothane† 2.4% | His bundle paced rhythm: Paired mean change ± SE |
|---|---|---|---|---|---|---|
| | | | msec | | | |
| RV$_a$ | 47.1 | 49.4 | 2.3 ± 0.4* | 50.1 | 53.0 | 2.9 ± 0.7* |
| LV$_a$ | 57.6 | 60.5 | 2.9 ± 0.5* | 62.2 | 65.9 | 3.7 ± 0.6* |
| LV$_b$ | 63.6 | 65.4 | 1.8 ± 0.6* | 68.2 | 70.4 | 2.2 ± 0.8* |

* Anesthetic related change significant $p \leq 0.05$ (paired $t$-test).

† Influence of anesthetic treatment significant $p \leq 0.05$ (ANOVA).

‡ Influence of location of site significant $p \leq 0.05$ (ANOVA).

**TABLE 2**

**Mean Epicardial Activation Times during Basal Thiopental Anesthesia and Basal Thiopental Anesthesia Plus 1.5% Halothane**

| Group II (N = 6) Epicardial recording site‡ | Atrial rhythm: Basal thiopental | Atrial rhythm: Thiopental plus 1.5% halothane | Atrial rhythm: Paired mean change ± SE | His bundle paced rhythm: Basal thiopental | His bundle paced rhythm: Thiopental plus 1.5% Halothane | His bundle paced rhythm: Paired mean change ± SE |
|---|---|---|---|---|---|---|
| | | | msec | | | |
| RV$_a$ | 47.9 | 49.6 | 1.7 ± 0.7 | 51.6 | 53.2 | 1.6 ± 0.7 |
| LV$_a$ | 54.1 | 54.5 | 0.4 ± 0.5 | 58.0 | 59.0 | 1.0 ± 0.6 |
| LV$_b$ | 58.8 | 59.0 | 0.2 ± 0.7 | 62.9 | 63.6 | 0.6 ± 0.7 |

‡ Influence of location of site significant $p \leq 0.05$ (ANOVA).

and 3, were also measured directly as a function of the prematurity at each recording site. The minimum interval between epicardial responses to the last of the series of paced beats and the following premature stimulus (minimum ERI) was determined at each site and defined as the functional refractory period (FRP) for the conduction pathway to each recording site.

Changes in measured parameters within each group were evaluated by an analysis of variance (ANOVA) to assess the influence of the His bundle pacing rate, anesthetic treatment, and location of the epicardial recording sites. Mean values and the results of testing the anesthetic-related changes with a paired $t$-test are shown in the Tables. A probability level of 0.05 or less was considered statistically significant.

## Results

Changes in epicardial activation times during regular (nonpremature) atrial and His bundle paced rhythms are shown in Tables 1 and 2. There was significant prolongation of EAT at 2.4 compared to 1.5% halothane concentrations (Table 1). The average increase at the three recording sites was 2.4 msec during atrial and 2.9 msec during His paced rhythms, respectively. In contrast, the addition of 1.5% halothane to basal thiopental anesthesia was associated with an insignificant increase in EAT averaging 0.9 msec (Table 2).

The His bundle pacing rate significantly affected the results of all parameters determined by the extrastimulus technique (Tables 3 to 6). Increasing the pacing rate decreased the effective and functional refractory periods and decreased conduction delays to the epicardium at the effective refractory period; however, these parameters were not significantly influenced by the location of the various recording sites over the range of rates studied.

Ventricular functional refractory periods significantly decreased with change to the higher halothane concentration in group I. The average decrease at each rate and recording site was 7.3 msec (Table 3). There was also a slight but insignificant decrease in FRP associated with the addition of 1.5% halothane to basal thiopental anesthesia averaging 1.4 msec (Table 4).

The effective refractory period did not decrease significantly at the higher halothane concentration in group I; however, the addition of halothane to basal thiopental anesthesia was associated with significant decrease in ERP averaging 9.1 msec (Tables 5 and 6).

TABLE 3

**Mean Ventricular Functional Refractory Periods at Two Levels of Halothane Anesthesia**

| Group I<br>N = 8<br>Epicardial recording site | His bundle pacing rate (bpm)§ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 125 | | | 150 | | | 175 | | |
| | Vol % halothane† | | Paired change ± SE | Vol % halothane† | | Paired change ± SE | Vol % halothane† | | Paired change ± SE |
| | 1.5% | 2.4% | | 1.5% | 2.4% | | 1.5% | 2.4% | |
| | msec | | | | | | | | |
| $RV_a$ | 237.5 | 229.2 | −8.3 ± 2.6* | 219.8 | 212.4 | −7.4 ± 1.8* | 203.4 | 199.1 | −4.3 ± 1.8 |
| $LV_a$ | 240.7 | 230.7 | −10.1 ± 2.0* | 222.5 | 213.7 | −8.8 ± 1.7* | 206.1 | 199.3 | −6.8 ± 1.7* |
| $LV_b$ | 232.2 | 228.1 | −8.2 ± 2.8* | 218.5 | 211.6 | −7.2 ± 2.1* | 203.1 | 198.2 | −4.9 ± 1.6* |

* Anesthetic related change significant $p \leq 0.05$ (paired $t$-test).

† Influence of anesthetic treatment significant $p \leq 0.05$ (ANOVA).

§ Influence of His bundle pacing rate significant $p \leq 0.02$ (ANOVA).

TABLE 4

**Mean Ventricular Functional Refractory Periods during Basal Thiopental Anesthesia and Basal Thiopental Anesthesia Plus 1.5% Halothane**

| Group II<br>N = 6<br>Epicardial recording site | His bundle pacing rate (bpm)§ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 125 | | | 150 | | | 175 | | |
| | Basal thiopental | Thiopental plus 1.5% halothane | Paired change ± SE | Basal thiopental | Thiopental plus 1.5% halothane | Paired change ± SE | Basal thiopental | Thiopental plus 1.5% halothane | Paired change ± SE |
| | msec | | | | | | | | |
| $RV_a$ | 251.6 | 249.8 | −1.7 ± 2.6 | 232.8 | 229.5 | −3.3 ± 3.0 | 214.6 | 213.2 | −1.5 ± 2.0 |
| $LV_a$ | 252.1 | 250.2 | −1.9 ± 4.6 | 232.5 | 229.9 | −2.4 ± 3.3 | 214.8 | 214.2 | −0.7 ± 2.4 |
| $LV_b$ | 249.9 | 247.4 | −2.5 ± 4.2 | 229.8 | 229.7 | −0.1 ± 3.7 | 212.3 | 213.7 | +1.3 ± 3.3 |

§ Influence of His bundle pacing rate significant $p \leq 0.02$ (ANOVA).

TABLE 5

**Effective Refractory Period of Ventricular Conduction System and Conduction Delays at Effective Refractory Period at Two Levels of Halothane Anesthesia**

| Group I<br>N = 8<br>Pacing rate | Effective refractory period | | | Conduction Delay‖ at effective refractory period | | |
|---|---|---|---|---|---|---|
| | Vol % halothane | | Paired change ± SE | Vol % Halothane¶ | | Paired change ± SE |
| | 1.5% | 2.4% | | 1.5% | 2.4% | |
| *beats/min* | msec | | | | | |
| 125 | 187.2 | 182.8 | −4.4 ± 3.5 | 58.0 | 51.6 | −6.4 ± 3.9 |
| 150 | 178.4 | 175.4 | −3.0 ± 2.2 | 47.3 | 41.1 | −6.2 ± 2.5* |
| 175 | 168.9 | 168.1 | −0.8 ± 2.2 | 40.7 | 35.1 | −5.6 ± 2.9 |

* Anesthetic related change significant $p \leq 0.05$ (paired $t$-test).

‖ Influence of location of site not significant (ANOVA); site averaged values shown.

¶ Influence of anesthetic treatment $0.05 \leq p \leq 0.07$ (ANOVA).

Conduction delays at the effective refractory period are also shown in Tables 5 and 6. Change to the higher halothane concentration in group I was consistently associated with a decrease in $CD_{ERP}$. The average decrease, 6.1 msec, was not statistically significant ($p \leq 0.07$) but would have reached significance had the average change been 6.2 msec. In contrast, the addition of halothane to basal thiopental anesthesia was associated with significant increase in $CD_{ERP}$ by an average of 9.6 msec.

## Discussion

Recent studies have demonstrated that halothane prolongs H-V intervals at high concentrations[4, 5] but does not prolong H-V intervals when given to animals initially anesthetized with pentobarbital.[6] In the cath-

**TABLE 6**

**Effective Refractory Period of Ventricular Conduction System and Conduction Delays at Effective Refractory Period during Basal Thiopental Anesthesia and Basal Thiopental Anesthesia Plus 1.5% Halothane**

| Group II<br>N = 6<br>Pacing rate | Effective refractory period | | | Conduction delay‖ at effective refractory period | | |
|---|---|---|---|---|---|---|
| | Basal thiopental | Thiopental plus 1.5% halothane† | Paired change ± SE | Basal thiopental | Thiopental plus 1.5% halothane† | Paired change ± SE |
| *beats/min* | | | *msec* | | | |
| 125 | 206.8 | 194.7 | −12.2 ± 4.6* | 52.9 | 67.0 | +14.1 ± 4.1 |
| 150 | 188.2 | 179.8 | −8.4 ± 2.0* | 52.7 | 61.1 | +8.4 ± 4.8 |
| 175 | 178.4 | 171.8 | −6.6 ± 1.6* | 43.1 | 49.4 | +6.3 ± 4.1 |

* Anesthetic related change significant $p \le 0.05$ (paired *t*-test).

† Influence of anesthetic treatment significant $p \le 0.05$ (ANOVA).

‖ Influence of location of site not significant (ANOVA); site averaged values shown.

eter recording techniques used in these studies, the H-V interval represents the portion of the P-R interval required for conduction of descending impulses from the His bundle through the His-Purkinje system to the interventricular septum. It is possible that the difference in results could be explained by a slight change in catheter position or by the different methods used to define the onset of septal activity in the two laboratories,[9] as well as by the presence of basal barbiturate anesthesia in one of the groups of animals.

We elected to reexamine the effects of halothane on ventricular conduction in the presence and absence of basal barbiturate anesthesia. The direct measurement technique employed in the present study is not subject to variations in catheter placement or interpretations of the onset of septal activity. This invasive technique provided the opportunity to assess halothane dose-related changes in ventricular conduction during both atrial and His bundle paced rhythms. In addition, a His bundle extrastimulus technique could be applied to assess changes occurring in the refractory periods of the ventricular conduction system. Thus, the methods used permitted evaluation of the hypothesis that halothane may simultaneously depress conduction and shorten refractory periods in the ventricular conduction system in a manner consistent with the actions of halothane on Purkinje fibers in vitro.

Interpretation of the present findings is limited in several respects. The experiment was not designed to determine differences in conduction and refractoriness between the control states of the two groups. Thus there was no significant difference between mean epicardial activation times or functional refractory periods of the group I animals at 1.5% halothane concentration and the group II animals during basal thiopental anesthesia (Students *t*-test for groups of different sample size). It was necessary to employ the paired design and variance analysis within each group due to the large between animal variations of all parameters. Changes in latency, the time required for the pacing stimulus to initiate a propagated His bundle response, may have influenced the determination of the effective refractory period and conduction delays at the effective refractory period; however, changes in latency do not influence the measurement of functional refractory periods in the ventricular conduction system in vitro.[10] Finally, although certain dose-related changes in the parameters measured were observed in each group, the changes are not necessarily due to direct effects of halothane. Changes in systemic blood pressure, ventricular volume, plasma ionic composition, blood pH, and $P_{CO_2}$, and changes in cardiac autonomic efferent activity were not systematically studied in this preparation but may have important influences on the parameters measured.

The functional significance of the conduction intervals and refractory periods measured deserves comment. The epicardial activation times determined in this study are analogous to H-V interval measurements with the exception that the EAT includes the time required for transmural conduction of the cardiac impulse from the endocardial Purkinje fibers to the epicardial recording sites. The effective refractory period is the interval between the last of a series of paced beats and the earliest premature His bundle stimulus which was able to propagate through the ventricular conduction system and activate the ventricles. At short coupling intervals premature His bundle stimuli are delayed or blocked as they encounter residual refractoriness in the wake of the previous paced beat at areas of maximal refractory period duration in the ventricular conduction system.[8, 10] In vivo, this occurs at a proximal major bundle branch level and the phenomenon is responsible for aberrant ventricular conduction of premature His bundle stimuli.[11, 12] The functional refractory period was defined as the minimum interval between epicardial responses to the last of a series of paced beats and the following premature stimulus. In vitro, measurements of functional refractory periods reflect the refractory period duration of the Purkinje fibers at the areas of maximal refractory period duration between the stimulation and recordings sites.[10]

The theoretical significance of these refractory periods may be related to their influence on the conduction of premature impulses from the bundle of His. Myerberg et al[10] have suggested that the ventricular conduction system protects against fibrillation by limiting the prematurity at which descending impulses traverse the ventricular conduction system to enter the more slowly conducting myocardium. Conduction delays at the effective refractory period ($CD_{ERF}$) were measured in the present study to assess the ability of the ventricular conduction system to delay activation of the epicardium by the earliest propagating His bundle stimulus.

The results in group I indicate that there was both depression of conduction and shortening of refractory period durations in the ventricular conduction system associated with change in halothane concentrations from 1.5% to 2.4%. The prolongation of epicardial activation times, a few milliseconds, was similar to the H-V interval prolongation noted by Atlee et al[5] at 2 and 3 MAC (minimal alveolar concentration) halothane anesthesia. Our findings, using an independent method, confirm the observation that halothane depresses ventricular conduction in vivo. The decrease in functional refractory periods observed with change from 1.5% to 2.4% halothane, about 7 msec, was small in comparison with the decrease in FRP found with increasing His bundle pacing rate. There was also no change in the effective refractory period and decrease in conduction delay of the most premature His bundle stimulus able to propagate to the ventricles. These in vivo findings are consistent with the reported effects of halothane on Purkinje fibers in vitro. They also support the hypothesis that halothane may facilitate the occurrence of reentrant arrhythmias in vivo by depressing conduction and shortening refractory periods in the ventricular conduction system.

The results in group II were obtained in the presence of basal thiopental anesthesia. The absence of prolongation of epicardial activation times upon addition of 1.5% halothane to basal thiopental anesthesia was similar to the absence of prolongation of H-V intervals noted by Morrow et al[6] with the addition of 1% or 2% halothane to basal pentobarbital anesthesia. There was no change in functional refractory periods, but a decrease in the effective refractory period and increased conduction delay of the most premature His bundle stimulus able to propagate to the ventricles. In vitro, pentobarbital is not associated with significant alterations of Purkinje fiber action potentials.[13]

In summary, the dose-related effects of halothane on conduction and refractoriness in the ventricular conduction system were determined in an open chest canine model. A change in halothane concentration from 1.5% to 2.4% was accompanied by evidence of depressed conduction, shortened ventricular functional refractory periods, and less delay of epicardial activation by the most premature propagating His bundle extrastimulus in a manner consistent with the reported actions of halothane on Purkinje fibers in vitro. In contrast, the addition of 1.5% halothane to basal thiopental anesthesia was not accompanied by evidence of depressed conduction or altered ventricular functional refractory periods. However, the effective refractory period of the ventricular conduction system decreased, and there was increased delay of epicardial activation by the most premature propagating His bundle extrastimulus. The results confirm previous reports that halothane depresses ventricular conduction in a dose-related manner and that halothane apparently does not depress ventricular conduction when it is added in moderate concentrations to basal barbiturate anesthesia. The findings in the absence of basal barbiturate anesthesia support the hypothesis that halothane may facilitate the occurrence of reentrant ventricular arrhythmias in vivo by simultaneously depressing conduction and shortening refractory period durations in the ventricular conduction system.

## ACKNOWLEDGMENTS

The authors are indebted to Dr. John Kalbfleisch of the Research Service of the Veterans Administration Hospital, Wood, Wisconsin, for his professional statistical assistance and to Dr Donald Pederson of the Department of Cardiology of the Medical College of Wisconsin for his helpful criticism.

## REFERENCES

1. Singer DH, Lazzara R, Hoffman BF: Interrelationships between automaticity and conduction in Purkinje fibers. Circ Res 21: 537–557, 1967
2. Sasyniuk BI, Mendez C: A mechanism for re-entry in canine ventricular tissue. Circ Res 28:3–15, 1971
3. Hausworth O: Effects of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 24:745–750, 1969

4. Atlee JL, Rusy BF: Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. Anesthesiology 36:112-118, 1972
5. Atlee, JL III, Homer LD, Tobey RE: Diphenylhydantoin and lidocaine modification of A-V conduction in halothane anesthetized dogs. Anesthesiology 43:49-59, 1975
6. Morrow DH, Logic JR, Haley JV: Antiarrhythmic anesthetic action. I. The effect of halothane on canine intracardiac impulse conduction during sinus rhythm. Anesth Analg 56:187-193, 1977
7. Hoffman BF, Moore EN, Stuckey JH, et al: Functional properties of the atrioventricular conduction system. Circ Res 13:308-328, 1963
8. Moe GK, Mendez C, Han J: Aberrant A-V impulse propagation in the dog heart: a study of functional bundle branch block. Circ Res 16:261-286, 1965
9. Narula OS: Validation of His bundle recordings: limitations of the catheter technique, in His Bundle Electrocardiography and Clinical Electrophysiology. Edited by OS Narula. Philadelphia, FA Davis Co, 1975, pp 65-93
10. Myerberg RJ, Steward JW, Hoffman BF: Electrophysiologic properties of the canine peripheral A-V conduction system. Circ Res 26:361-378, 1970
11. Zipes DP, Knope RF, Mendez C, et al: The site of functional right bundle branch block in the intact canine heart. Adv Cardiol 14: 105-114, 1975
12. Lazzara R, El-Sherif N, Beeler B, et al: Regional refractoriness within the ventricular conduction system. Circ Res 39:254-262, 1976
13. Rosen MR, Gelband H, and Hoffman BF: Effects of blood perfusion on electrophysiological properties of isolated canine Purkinje fibers. Circ Res 30:575-585, 1972

---

## Blood Flow during Cardiopulmonary Resuscitation

Despite the widespread clinical application of cardiopulmonary resuscitation (CPR), the mechanism responsible for blood flow during this maneuver remains undefined, although it has been assumed that blood is squeezed from the heart by direct compression of the sternum. The hemodynamics of CPR was studied in 15 arrested dogs. During chest compression, pressures in the left ventricle, aorta, right atrium, and pulmonary artery were essentially identical. These pressures were also equal to the intrathoracic pressure as estimated by an esophageal balloon catheter. Unequal transmission of pressures to the extrathoracic arterial and venous system resulted from collapse of the great veins at the thoracic outlet as intrathoracic pressures rose. This phenomenon gave rise to a peripheral arteriovenous pressure gradient and antegrade flow. When intrathoracic pressure was increased by maintaining the lungs fully inflated during chest compression, aortic systolic pressure rose from 27.3 ± 4.0 mm Hg to 58.4 ± 7.9 mm Hg ($p < 0.001$), and carotid blood flow increased from 9.0 ± 2.2 ml/min to 28.6 ± 5.9 ml/min ($p < 0.001$). Increasing the intrathoracic pressure by tightly binding the abdomen to prevent paradoxical diaphragmatic motion during chest compression also resulted in an increase in aortic systolic pressure, from 29.4 ± 3.2 to 57.7 ± 7.7 mm Hg ($p < 0.001$), and an increase in carotid blood flow, from 14.5 ± 8.1 ml/min to 32.3 ± 9.7 ml/min ($p < 0.005$). It appears that pressure generation and blood flow during CPR in the dog result from a generalized rise in intrathoracic pressure, not from direct cardiac compression. Maneuvers that raise the intrathoracic pressure can dramatically increase carotid blood flow during CPR. (*Rudikoff MT, Maughan WL, Effron M, et al: Mechanisms of blood flow during cardiopulmonary resuscitation. Circulation 61:345-352, 1980*)

ANESTH ANALG
59:335–340, 1980

# Dextran-Local Anesthetic Interactions

James E. Scurlock, MD, and Benson M. Curtis, MS

SCURLOCK, J. E., AND CURTIS, B.: Dextran-local anesthetic interactions. Anesth Analg 59: 335–340, 1980.

A number of clinical investigators have found that low molecular weight (LMW) dextran prolongs the action of local anesthetics on peripheral nerve. Other reports indicate no significant change in duration with these combinations. We performed a series of experiments to determine if LMW dextran interacted with lidocaine or bupivacaine so that the duration of block would be enhanced. Millipore filtration, equilibrium dialysis, and membrane ultrafiltration were performed with $^{14}$C-lidocaine in the presence and absence of LMW dextran to determine whether any binding existed between LMW dextran and lidocaine which might prolong a block by retarding the egress of the local anesthetic. In all cases, the lidocaine crossed the 8,000 to 10,000 molecular weight barriers as quickly with LMW dextran as without it. To confirm these findings in vivo, $^{14}$C-lidocaine, with and without 5% LMW dextran, was infused into the infraorbital nerve of rats. Thirty minutes after the block was established, the animals were killed and the nerves removed and sectioned. The amount of lidocaine still present was the same whether or not LMW dextran was added. If the amount of lidocaine present is not altered, then its effect must be enhanced if a prolonged block is to be produced. Increased refractory period would increase the effect of a given concentration of lidocaine or other local anesthetic on the transmission of noxious stimuli. LMW dextran 5% did not increase the block of 0.25 mM lidocaine on frog sciatic in vitro at frequencies from 1 to 100 Hz. Direct assessment of the effect of LMW dextran was made by injecting 1 mg of bupivacaine or 2 mg of lidocaine with or without 5% LMW dextran into the rat maxillary nerve and assessing the duration of nerve block. In both cases, block duration was the same whether or not dextran was added. These data suggest that LMW dextran does not affect the kinetics of lidocaine nor does it enhance the action of lidocaine or bupivacaine in other ways, and thus these data support the findings of those who see no prolongation of action when LMW dextran is added to lidocaine or bupivacaine.

**Key Words:** ANESTHETICS, Local: dextran interactions; BLOOD: dextran-local anesthetic interactions.

WHETHER or not the duration of local anesthetic action is prolonged by the addition of low molecular weight (LMW) dextran is controversial. Bridenbaugh[1] found 5% LMW dextran prolonged by only 5% the duration of intercostal nerve block produced by 0.375% bupivacaine. Contrarily, Kaplan et al[2] reported a 200% increase in the duration of intercostal block when dextran was added to 0.75% bupivacaine. Similar discrepancies have occurred when LMW dextran has been combined with other local anesthetics. In an attempt to resolve these discrepancies, we used a number of in vivo and in vitro preparations to evaluate the possible interactions between LMW dextran and local anesthetics. The tests were chosen for their pertinence to the question and their ability to give objective, reproducible answers. It was hoped that the results would collectively provide data for or against the possible ability of dextran to modify local anesthetic action. If dextran were found to influence this action, then fuller appreciation of the mechanism might allow us to understand the seemingly inconsistent results of clinical studies and so manipulate these mechanisms to prolong local anesthetic drug action.

---

Supported by National Institutes of Health grant R23 GM 24164.

Received from the Department of Anesthesiology, Virginia Mason Research Center, Seattle, Washington 98101. Accepted for publication January 29, 1980.

Reprint requests to Dr. Scurlock, Department of Anesthesia, The Mason Clinic, 1100 Ninth Avenue, Seattle, Washington 98101.

## Materials and Methods

### Millipore Filtration

A mixture of 26 mM $^{14}$C-lidocaine-HCl ($1.9 \times 10^{-3}$ µCi/mM), 1:1 (v/v), and LMW dextran (10% w/v), or 2 mM bovine serum albumin (BSA), or distilled water was incubated at 37 C for 15 minutes. Samples were then filtered across a Millipore pellicon membrane disc (10,000 MW cutoff), and the discs washed three times with distilled $H_2O$. Filters were dried and placed face up in 5 ml of Aquasol II LSC cocktail (New England Nuclear) and counted on a PRIAS LSC (Packard Instruments) for 10 minutes. Counts were corrected for background and nonspecific quenching.

### Equilibrium Dialysis

A mixture of 26 mM $^{14}$C-lidocaine-HCl ($1.9 \times 10^{-3}$ µCi/mM), 1:1, and either 10% LMW dextran, 2 mM BSA, or distilled $H_2O$. Two milliliters of solution was placed inside an 8-cm length of 0.75-cm diameter dialysis tubing (VWR Scientific 8,000 MW cutoff), suspended in 48 ml of distilled $H_2O$, and equilibrated for 24 hours at 37 C. Two 1-ml aliquots from inside and outside the dialysis tubing were added to 5 ml of Aquasol II and counted. Counts were corrected for background and quenching.

### Membrane Ultrafiltration

LMW dextran (10%), $H_2O$, or 2 mM BSA were mixed 1:1 with 10 µM or 25 mM $^{14}$C-lidocaine ($2.2 \times 10^{-2}$ µCi). Five milliliters of solution was placed inside ¼-in dialysis tubing (VWR Scientific 8000 MW cutoff) and suspended inside a 12-ml conical tube, held in place by a ground-glass stopper. The tube was centrifuged at 500 × *g* for 2 hours in a clinical bench centrifuge at 20 C. Aliquots (1 ml) were removed from the tubing; the ultrafiltrate was collected from the centrifuge tube, and both were counted in Aquasol II.

### In Vivo Kinetics

Sprague-Dawley rats (300 to 400 g) were lightly anesthetized with pentobarbital (10 mg IP). LMW dextran (10%) was mixed 1:1 with $^{14}$C-lidocaine 1% (w/v), and 0.2 ml of this mixture (2 mg of lidocaine with $5 \times 10^{-2}$ µCi) was injected about the infraorbital nerve using a 30-gauge needle guided by a metal mouth jig as described previously by Fink et al.[3] Sensory block was always established within 1 minute, thus confirming accurate placement of the local anesthetic. Thirty minutes after the block was established, the animals were killed and a 16-mm section of the infraorbital nerve in the vicinity of the injection site was removed and divided into four 4-mm sections. The nerve was washed in 0.9% NaCl to remove drug not bound to tissue. The sections of nerve were solubilized in 0.5 ml of solvene 350 (Packard Instruments) and counted in 4.5 ml of Aquasol II.

### Frequency Effect

Northern *Rana pipiens* frogs were decapitated and pithed, and the sciatic nerve was carefully dissected from adjoining muscle and connective tissue from the spinal cord to the lower part of the leg. Nerves were kept moist by application of frog Ringer's solution (100 mM NaCl, 2.5 mM KCl, 1.8 mM $CaCl_2$, 111 mM glucose, and 10 mM $Na^+$-phosphate buffer, pH 7.2) and the outer sheath of connective tissue (epineurium) was removed with fine needles under a dissecting microscope while the field was illuminated by indirect fluorescent light. Nerves were placed in a sucrose-gap nerve chamber containing five 9-mm sections separated by Vaseline seals. Ringer's solution was placed in each section except in the section between the recording electrodes which contained isotonic sucrose. Drug or Ringer's solution was perfused through the chamber between stimulating and recording electrodes at a rate of 20 ml/hr. Drug consisted of 0.25 mM lidocaine in frog Ringer's or 0.5 mM lidocaine in frog Ringer's mixed 1:1 with LMW dextran (v/v) 10% (w/v). To determine the frequency dependence of drug block, a computer (Digital Declab 11/03) was programmed to deliver a train of pulses logarithmically increasing from 1 Hz to 100 Hz in 10 seconds. Output pulses were stretched by a pulse shaper and used to trigger a stimulus isolation unit (Digitimer LTD, model DS2) which controlled the stimulus amplitude (0.5 to 1.0 V) and duration (0.1 millisecond). Compound action potentials were amplified (Tektronix AM502) and displayed along with the stimulus train on oscilloscope (Tektronix 5111). Relevant trains of compound action potentials were stored and photographed (CSB oscilloscope camera Tektronix) (see Fig 1).

### Duration of Nerve Block in Vivo

Male Sprague-Dawley rats weighing 300 to 400 g each were given intraperitoneal injections of 10 mg of sodium pentobarbital after a light ether induction. Additional pentobarbital was given, if necessary, until the righting reflex was lost. Bupivacaine-HCl 0.75% or lidocaine-HCl 2.0% was mixed 1:1 (v/v) with LMW

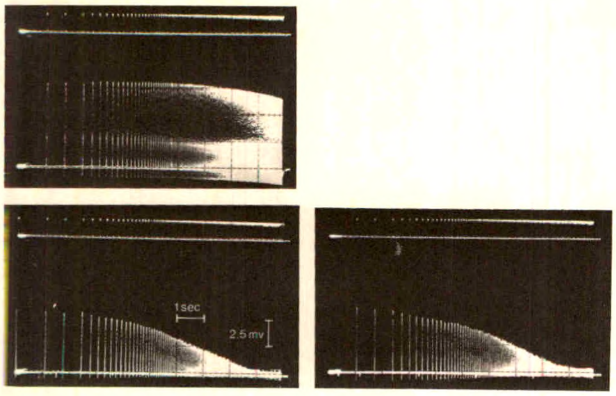


FIG 1. Upper trace in each section, train of stimuli; lower trace, train of action potentials; upper section, control; lower left, 0.25 mM lidocaine in Ringer's solution, lower right, 0.5 mM lidocaine in Ringer's solution mixed 1:1 with LMW dextran. See text for details.

dextran 10% (w/v) or deionized water. An injection of 1 mg of bupivacaine (0.26 ml) or 2 mg of lidocaine (0.2 ml) with or without dextran was given about the maxillary nerve through a 30-gauge needle guided to the nerve by a metal jig positioned on the roof of the mouth by the molar.[3] The contralateral maxillary nerve was used as a control throughout the experiment. Block was tested by stimulating the lip/whisker area innervated by the maxillary nerve on experimental and control sides and observing whether the stimulus produced a contraction of abdominal muscles or not. Stimulation consisted of 1 to 10 V, 6-millisecond square wave pulse trains (two pulses per second for 5 seconds) produced by a Grass S48 stimulator triggering a stimulus isolation unit (DS-2, Digitimer Ltd) delivered through bipolar electrodes (two 30-gauge needles 2 mm apart). The response was quantitated by recording the electromyogram (EMG) from muscles of the abdominal wall and displaying it on a Tektronix 5111 oscilloscope after amplification (Tektronix AM502 differential amplifier). Comparison of the EMG response produced by stimulating the control side and treated side allowed an accurate determination of the duration of maxillary nerve block (see Fig 2).

## Results

### Millipore Filtration

Results are summarized in Table 1. Dextran, which is too large to cross the Millipore filter, did not increase the amount of lidocaine trapped by the filter, whereas albumin, which is known to bind lidocaine, did.

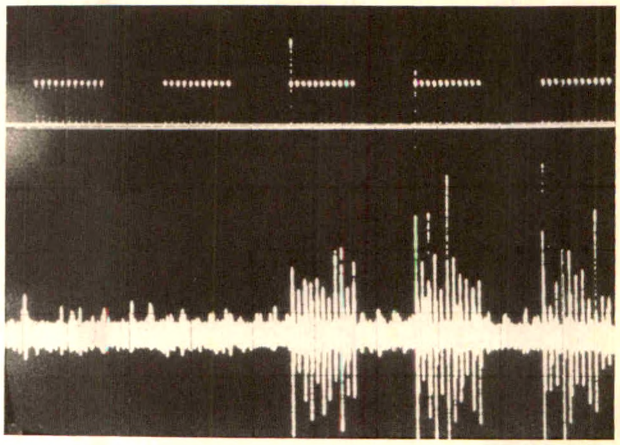


FIG 2. Upper trace, train of stimuli; lower trace, abdominal wall EMG activity. First two trains of stimuli are applied to the side injected with 0.75% bupivacaine and last three trains are to control unanesthetized side. See text for details.

**TABLE 1**

**Effect of Dextran and Albumin on Millipore Filtration of $^{14}$C-Lidocaine***

| | Bound CPM |
|---|---|
| $^{14}$C-lidocaine | 242 (2) |
| $^{14}$C-lidocaine-dextran | 203 (2) |
| $^{14}$C-lidocaine-albumin | 1,936 (2) |

* Values are means of two experiments. CPM, Counts per minute.

**TABLE 2**

**Effect of Albumin and Dextran on Equilibrium Dialysis of $^{14}$C-Lidocaine***

| | CPM inside | CPM outside |
|---|---|---|
| $^{14}$C-lidocaine | 1,853 ± 95 | 866 ± 30 |
| $^{14}$C-lidocaine-dextran | 1,847 ± 126 | 957 ± 32 |
| $^{14}$C-lidocaine-albumin | 2,820 ± 53 | 991 ± 13 |

* Values are means of four determinations ± SD.

### Equilibrium Dialysis

Results are summarized in Table 2. The LMW dextran-lidocaine sample showed a 1% decrease in counts per minute (CPM) bound inside the tubing compared to control values while the albumin-lidocaine sample showed a 54% increase in bound counts per minute compared to control values. The increased total counts appear to result from the ability of albumin to compete with the dialysis membrane as a binding site for lidocaine.

### Membrane Ultrafiltration

Results are summarized in Table 3. Again the LMW dextran-lidocaine mixture is kinetically essentially the

**TABLE 3**

**Effect of Albumin and Dextran on Membrane Ultrafiltration of $^{14}$C-Lidocaine***

| | 10 μM | | 25 mM | |
|---|---|---|---|---|
| | CPM inside | CPM outside | CPM inside | CPM outside |
| $^{14}$C-lidocaine | 6,442 ± 43 | 10,236 ± 638 | 8.039 ± 26 | 8,987 ± 369 |
| $^{14}$C-lidocaine-dextran | 6,384 ± 110 | 10,909 ± 757 | 7,558 ± 30 | 8,945 ± 282 |
| $^{14}$C-lidocaine-albumin | 9,433 ± 244 | 7,215 ± 343 | 9,474 ± 100 | 8,460 ± 236 |

* Values are means of four determinations ± SD.

same as the water-lidocaine combinations, whereas albumin binding shows a distinct effect. This and the previous two studies indicate no binding between LMW dextran and lidocaine. The additional concentration of lidocaine (10 μM) was to assure that we were not missing small effects due to saturation of dextran.

### In Vivo Kinetics

Results are summarized in Table 4. There was no significant difference in the kinetics of lidocaine on peripheral nerve in the presence or absence of dextran.

### Frequency Effect

As can be seen in Fig 1, 0.5 mM lidocaine had no greater effect on frequency response with the dextran than without it.

### In Vivo Block

Results are summarized in Table 5. The onset time refers to the period from the injection of the anesthetic to the loss of EMG response on the treated side (see Fig 2). Duration of anesthesia represents the time from the onset of the block to the time when the EMG response from the control and treated sides were again similar. There was no statistically significant effect of LMW dextran on either onset or duration of nerve block produced by bupivacaine or lidocaine.

**TABLE 4**

**In Vivo Kinetics of $^{14}$C-Lidocaine and $^{14}$C-Lidocaine-Dextran Mixture***

| | Bound lidocaine (ng)/tissue (mg) in section | | | |
|---|---|---|---|---|
| | 1 | 2 | 3† | 4 |
| Lidocaine | 282 ± 73 | 450 ± 107 | 1,086 ± 381 | 2,000 ± 662 |
| Lidocaine-dextran | 313 ± 94 | 559 ± 189 | 964 ± 350 | 2,076 ± 337 |

* Values are means of seven determinations ± SD.

† Approximate injection site.

**TABLE 5**

**Effect of Dextran on Bupivacaine and Lidocaine Anesthesia of Rat Maxillary Nerve***

| Treatment | Onset of block | Duration of block |
|---|---|---|
| Bupivacaine (1 mg) | 1 min ± 2 sec | 134 min ± 24 sec (5)* |
| Bupivacaine (1 mg) + LMW dextran | 1 min ± 2 sec | 131 min ± 26 sec (6)† |
| Lidocaine (2 mg) | 1 min ± 1 sec | 105 min ± 23 sec (5)‡ |
| Lidocaine (2 mg) + LMW dextran | 1 min ± 1 sec | 102 min ± 10 sec (5) |

* Values are means ± SD. Number of animals is shown in parentheses.

† *p* value for the bupivacaine groups is 0.999 as calculated by Student's *t*-test.

‡ *p* value for the lidocaine group is 0.997.

## Discussion

The doubling or tripling of the duration of action of a long-acting local anesthetic such as bupivacaine would greatly enhance our ability to deal effectively with acute and chronic pain. Profound relief from pain of upper abdominal surgery or thoracotomy can be achieved with intercostal block but the lack of ultra-long-acting local anesthetics has kept the full potential of this and other nerve block techniques from being realized. We were unable, however, to discover any effect of LMW dextran on local anesthetics. In three in vitro and two in vivo preparations, we could find no evidence that LMW dextran directly or indirectly affects the kinetics of action of local anesthetics on peripheral nerve. $^{14}$C-lidocaine moved across dextran barriers just as easily in the presence or dextran as in its absence. Furthermore, dextran had no effect on the rate at which $^{14}$C-lidocaine concentration decreased at the site of injection.

The lack of influence of dextran on the kinetics of local anesthetics also indicates that dextran has no vasoactive properties. Other evidence for this is the lack of hemodynamic changes seen when dextran is given in large doses by vein (for improvement of microcirculation). Dextran has been shown not to have any local anesthetic activity.[2] We confirmed this in our in vitro frog sciatic preparation and further showed that dextran did not enhance the blocking action of lidocaine at low or high frequencies. The lack of frequency effect indicates that dextran does not enhance the ability of a local anesthetic to block noxious stimuli.[4]

Does LMW dextran cause changes in the pH value or osmolarity of interstitial fluid, which in turn might affect local anesthetic action? We conclude that LMW dextran probably does not cause such changes. Dextran is a sugar and does not ionize at physiologic pH. Therefore, it should have little if any effect on interstitial pH even though the pH of dextran 40 is 8. Likewise, the 50-g/L of dextran in the 1:1 mixture of 10% LMW dextran and local anesthetic increases the osmolality by only 1.25 mosmol (less than 0.5% of normal interstitial fluid).

In order to eliminate the possibility of other unknown mechanisms, we simply determined the duration of infraorbital block in 21 rats. The method used has a discrete and objective end point. Even though the number of experiments was relatively small, the results were so consistent that, according to Student's *t*-test, there is only one chance in 1000 that the mean duration of bupivacaine anesthesia was not the same whether LMW dextran was present or not. This value is three in 1000 for lidocaine. The rapid, consistent onset times indicate accurate placement of the drug.

Binding of a local anesthetic drug to LMW dextran or some other complex would also retard its uptake and thus change the duration of anesthesia because binding would reduce the amount of drug available for interaction with the nerve. We found this to be the case with albumin but not dextran. Maxillary block with 1 mg of bupivacaine in 1 mM albumin had half the duration as the same block with 1 mg of bupivacaine in 5% LMW dextran or normal saline. We conclude that dextran has little if any effect on the action of local anesthetics.

What about the clinical studies? Were they wrong? Kaplan et al[2] found a 200% increase in intercostal block duration when 10% dextran was added (1:1) to 0.75% bupivacaine. Others have not observed such results. Bridenbaugh[1] found that the same combination of drugs increased the duration of intercostal block in man only 5% above that attained without dextran. The block techniques were different in the two studies (Kaplan et al used pinprick and Bridenbaugh used Allis forceps pinch), but it is unlikely that either of these factors caused the disparity in outcome. Otherwise, the results with bupivacaine without LMW dextran would not have been so close together in the two studies (Kaplan et al, 12 hours; Bridenbaugh, 12 hours 10 minutes). There were, however, two differences in these studies that were possibly significant. First, Kaplan et al had only six patients in each group; Bridenbaugh had fifty-seven patients. Second, Bridenbaugh's patients served as their own controls by having a different combination on each side, the side in which the dextran was injected being determined by a random selection table. The large number of patients, the internal control, and the random selection all make Bridenbaugh's study highly creditable.

Other human studies show less increase in duration of anesthesia with addition of LMW dextran than did the study of Kaplan et al. Chinn and Wirjoatmadja[5] found that dextran prolonged the action of tetracaine only 10% to 20% in blocks of the ulnar nerve. Also using ulnar nerve blocks, Nolte et al[6] found the duration of block with mepivacaine was increased 30% to 40% by dextran. This is far less than the 200% reported by Kaplan et al.

A most extensive and enlightening human study was that by Krömer[7] in which bilateral ulnar nerve blocks were given with a local anesthetic on one side and the same concentration of the local anesthetic with 3% dextran (60,000 MW) on the other side. The duration of analgesia, motor block, and temperature rise (>1.5 C) was then measured. The relevant data for lidocaine and bupivacaine are summarized in Table 6. An increase in lidocaine's sensory block of 42% was found ($p < 0.001$) but the increase was only 5% for bupivacaine ($p > 0.20$). The findings for dextran resemble those of adding epinephrine to a local anesthetic (Tucker et al[8]), i.e., the short-acting drugs are affected to a greater extent than the long-acting drugs. But we could find no evidence that dextran had any effect on kinetics, which is the presumed method by which epinephrine works to prolong anesthetic action. Even more perplexing is the fact that neither we nor others[9] could show any prolongation with lidocaine

**TABLE 6**

**Effect of Dextran on Duration of Ulnar Nerve Block with Bupivacaine and Lidocaine (adapted from Krömer[7])**

| Block | Without dextran | With dextran | *p* value* |
|---|---|---|---|
| Bupivacaine | | | |
| Sensory | 579.81 ± 93.8 | 613.7 ± 129.6 | >0.20 |
| Motor | 593.0 ± 90.6 | 602.8 ± 131.9 | >0.20 |
| Sympathetic | 607.83 ± 115.0 | 633.8 ± 115.8 | >0.20 |
| Lidocaine | | | |
| Sensory | 76.8 ± 8.2 | 108.2 ± 13.4 | <0.001 |
| Motor | 82.2 ± 15.1 | 99.8 ± 22.9 | <0.10 |
| Sympathetic | 88.8 ± 19.0 | 125.0 ± 11.5 | <0.005 |

* *p* values calculated from Krömer.[7]

in the rat maxillary preparation. Of note here is the fact that in Krömer's ulnar nerve experiments the bupivacaine block was approximately seven times longer than the lidocaine block, whereas in the rat maxillary preparation there was only a 20% increase with bupivacaine. The shorter duration seems likely to be a function of rapid uptake in the more vascular maxillary area. Perhaps no effect is seen from the dextran because it is also taken up rapidly. In the ulnar nerve block the dextran may be present long enough to affect lidocaine's action but gone when the bupivacaine begins to wear off. In other words, dextran must be present to exert an effect on neural conduction, and its relative absorption (relative to lidocaine, that is) is faster in the maxillary area than in the ulnar nerve area. If this is the case, then dextran must have an effect which we, and others, have been unable to detect.

In summary, we found that LMW dextran does not influence the in vitro or in vivo kinetics of local anesthetics, that LMW dextran is not a local anesthetic, and that LMW dextran neither enhances nor inhibits the action of local anesthetics on peripheral nerve. These findings are in agreement with those of Bridenbaugh[1] and Krömer,[7] i.e., the addition of LMW dextran to bupivacaine for the prolongation of block is not justified. Although the prolongation of other local anesthetics such as lidocaine, mepivacaine, etc, is still in doubt, the point is moot, as the desired results can be achieved with bupivacaine.

## REFERENCES

1. Bridenbaugh LD: Does the addition of low molecular weight dextran prolong the duration of action of bupivacaine? Regional Anesthesia 3:6, 1978
2. Kaplan JA, Miller ED Jr, Gallagher EG: Postoperative analgesia for thoracotomy patients. Anesth Analg 54:773–777, 1975
3. Fink BR, Aasheim G, Kish SJ, et al: Neurokinetics of lidocaine in the infraorbital nerve of the rat in vivo: relation to sensory block. Anesthesiology 42:731–736, 1975
4. Scurlock JE, Meymaris E, Gregus J: The clinical character of local anaesthetics: a function of frequency-dependent conduction block. Acta Anaesth Scand 22:601–608, 1978
5. Chinn MA, Wirjoatmadja K: Prolonging local anaesthesia. Lancet 2:835, 1967
6. Nolte H, Puente-Eqido JJ, Dudeck J, et al: Wirkungsverlangerung der Lokalanesthesie durch Dextran 6%. Anaesthesist 16: 221–224, 1967
7. Krömer B: Untersuchungen über der Einfluss von Dextran 6% (Macrodex) auf die Wirkungsdauer verschiendener Lokalanaesthetika. Inaugural-Dissertation zur Erlangung der Doctor Wurde der Hohen Medizinischen Fakultat der Johannes Gutenberg-Universtat, Mainz, 1969
8. Tucker GT, Moore DC, Bridenbaugh PO, et al: Systemic absorption of mepivacaine in commonly used regional block procedures. Anesthesiology 37:277–287, 1972
9. Buckley FP, Fink BR: The duration of action of nerve blocks produced by local anesthetic:dextran mixtures. Anesthesiology 51:S215, 1979

ANESTH ANALG
59:341-349, 1980

# Changes in Respiratory Pattern Affect Dead Space/Tidal Volume Ratio during Spontaneous but not during Controlled Ventilation: A Study in Pediatric Patients

**D. K. Rose, MD,* and A. B. Froese, MD, FRCP (C)†**

---

ROSE, D. K., AND FROESE, A. B.: Changes in respiratory pattern affect dead space/tidal volume ratio during spontaneous but not during controlled ventilation: a study in pediatric patients. Anesth Analg 59:341–349, 1980.

It is assumed in many gas exchange equations that dead space ($V_D$) is a constant fraction of tidal volume ($V_T$) during anesthesia despite variations in respiratory pattern. We tested this assumption by measuring $V_D/V_T$ ratios, using samples of mixed expired gas and arterial blood in 20 healthy anesthetized children (aged 1 to 17 years), divided into three groups. Group 1 was intubated; ventilation was controlled; total minute ventilation was held constant; and frequency (f) varied from 10 to 30/minute. Group 2 was intubated; breathing was spontaneous; and pattern was altered from fast and shallow to slow and deep. Group 3 was given mask anesthesia; breathing was spontaneous; and $V_D/V_T$ was measured at fast frequency only. The inter-relationships of dead space to tidal volume varied with the type of ventilation. In group 1 $V_D$ increased in direct proportion to $V_T$ (mean slope 0.25 ± 0.05; $p < 0.001$). In group 2, $V_D$ was smaller and remained constant despite alterations in tidal volume (mean slope 0.09 ± 0.09; $p > 0.05$). Although $V_D/V_T$ at the fast frequency was similar in the two groups, i.e., 0.35 in group 1 ($f = 30$) and 0.36 in group 2 ($f = 35.6$), differences became evident at slower frequencies. For a 50% reduction in frequency, $V_D/V_T$ decreased only 15% during controlled ventilation, but 41% during spontaneous respiration. During mask anesthesia (group 3) $V_D/V_T$ at a mean frequency at 29.4 was 0.55. For group 2 $V_D$ per kilogram was related to age by the equation $V_D/\text{kg} = 1.72 - 0.06$ (age in years) ml at the fast frequency of 35.6 ($n = 7$; $r = 0.73$). The equation at a slower frequency of 23.2 was not significantly different. During mechanical ventilation the dead space volume was always larger than during spontaneous breathing and in addition was rate dependent. At $f = 30$ $V_D/\text{kg} = 2.78 - 0.10$ (age in years) ml ($n = 7$, $r = 0.80$); at $f = 10$, $V_D/\text{kg} = 6.74 - 0.25$ (age in years) ml ($n = 7$; $r = 0.83$). These measurements demonstrate that in children with spontaneous respiration, increases in tidal volume are distributed to perfused lung regions with a net decrease in $V_D/V_T$ ratio. In contrast, with controlled ventilation wasted ventilation increases as $V_T$ is increased with no net change in $V_D/V_T$ ratio.

**Key Words:** VENTILATION: pediatric; ANESTHESIA: pediatric.

---

[*] Research Fellow, Department of Anesthesia, University of Toronto. Hospital for Sick Children.

[†] Assistant Professor, Department of Anesthesia, University of Toronto. and Research Institute, Hospital for Sick Children.

Received from the Department of Anesthesia, University of Toronto, and Hospital for Sick Children, Toronto, Ontario, Canada. Accepted for publication January 31, 1980.

Reprint requests to Dr. A. B. Froese, Room 4531, Respiratory Physiology Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

ALTHOUGH wasted ventilation is an important factor affecting the adequacy of gas exchange, dead space has not been carefully measured in children during general anesthesia. Instead we rely on data extrapolated from adults[1] and dogs[2] which indicate that dead space varies proportionally with tidal volume. These two studies indicate that dead space volume increases with increasing tidal volume and decreases with decreasing tidal volume. Both studies conclude that the respiratory system maintains a constant ratio of dead space and tidal volume despite changes in breathing pattern so that the impact on gas exchange of increases or decreases in tidal volume is minimized. However, the respiratory patterns of these adults and dogs were quite homogeneous. The breathing pattern of anesthetized children is, however, subject to wide variations in rate and tidal volume depending on the mode of ventilation, the degree of surgical stimulation, and the anesthetic. This made us question whether the maintenance of a constant ratio of dead space to tidal volume was a valid assumption in children. Therefore, in this study of healthy anesthetized children, we measured the dead space as a function of tidal volume over a wide range of respiratory patterns. Ventilation was both controlled and spontaneous and measurements were made with both mask anesthesia and following endotracheal intubation.

## Methods

Following approval of the protocol by the University of Toronto's Human Experimentation Committee, 20 children (aged 1 to 17 years) were studied in the supine position during elective surgical procedures. Informed consent was obtained from a parent. Preoperative Allen's tests confirmed the patency of both ulnar and radial arteries. All children were free from cardiopulmonary disease.

ABBREVIATIONS

| | |
|---|---|
| $V_D$ | Total dead space (ml) calculated using the Bohr equation corrected only for the volume of experimental apparatus used to make the measurements |
| $V_{D_{APP}}$ | Essential anesthetic apparatus dead space (ml) including the endotracheal tube and the connector that are essential for interfacing the patient and an anesthetic circuit |
| $V_{D_{ST}}$ | Subendotracheal tube (intrapulmonary) dead space (ml) = $V_D - V_{D_{APP}}$ |
| $V_T$ | Tidal volume (ml) |
| $\dot{V}_E$ | Minute volume (ml/min) |
| $V_D/V_T$ | Ratio of total dead space to tidal volume |
| $V_{D_{ST}}/V_T$ | Ratio of subendotracheal tube dead space to tidal volume |
| I:E | Ratio of the duration of inspiration to that of expiration |
| f | Frequency-breaths per minute |
| $Pa_{CO_2}$ | Arterial carbon dioxide tension (torr) |
| $P\bar{E}_{CO_2}$ | Mixed expired carbon dioxide tension (torr) |

Patients fasted at least 4 hours prior to induction of anesthesia and no premedication was used. Anesthesia was induced with intravenous thiopental (4 to 5 mg/kg) to which atropine (0.02 mg/kg; maximum, 0.6 mg) was added. Endotracheal intubation with an appropriately sized cuffed tube, if performed, was facilitated by succinylcholine (1 to 2 mg/kg). All tubes were precut for normal children to such a length as to position the distal tip midway between the larynx and carina with the proximal end 1 cm beyond the mouth. Nitrous oxide-oxygen (50% mixture) and an inhalation agent (halothane or enflurane) with or without a narcotic (meperidine or fentanyl) were used to maintain anesthesia during spontaneous ventilation. *d*-Tubocurarine or pancuronium bromide was administered when ventilation was controlled. Each patient was monitored using a precordial stethoscope, blood pressure manometer, and rectal temperature probe. Intravenous fluids were administered throughout the procedure to replace the calculated preoperative deficit and estimated surgical losses. After induction a 22-gauge Teflon catheter was inserted into the radial artery and flushed intermittently with a heparin solution (1 unit/ml).

During spontaneous ventilation the circuit included: a source of fresh gas which was drawn from a 5-L reservoir bag through a demand valve; a two-way Sierra valve (Sierra Engineering Co, Sierra Madre, CA), pretested at both high and low pressures for competence of the inspiratory and expiratory valves: a heated Fleisch pneumotachograph with automatic integration of the flow trace, (#1; volume 12 ml); and either a standard tight-fitting face mask or an endotracheal tube. The resistance of the entire circuit was 0.1 cm $H_2O$/L/min. The ventilator, a Volgyesi[3] constant flow, volume-cycled ventilator, allowed passive expiration during controlled ventilation and the precise separation of inspired and expired gases. The ratio between the duration of inspiration and expiration (I:E) was fixed at 1:2 for all patients and the flows and volumes were recorded by a pneumotachograph placed between the ventilator valve and endotracheal tube. Flow pattern, tidal volume, and frequency were recorded on a polygraph.

Intubated patients were divided into two groups, those whose ventilation was controlled (group 1: n =

10, age = 8.7 ± 5.6 years) and those who were allowed to breath spontaneously (group 2: n = 12, age = 7.8 ± 4.6 years). The pattern of ventilation in seven children of both groups was deliberately altered during the surgical procedure. For the seven patients in group 1 (age = 7.6 ± 5.5 years) the frequency and tidal volume were varied by adjusting the ventilator. All those patients were ventilated at frequencies of 10, 15, and 30 breaths per minute and one patient at a fourth value of 40 breaths per minute. For each patient the total minute ventilation and ratio of inspiratory and expiratory duration were kept constant. In the children in group 2 halothane was used to produce a rapid shallow pattern of spontaneous ventilation. A slow deep pattern was achieved in seven of these 12 patients (age = 9.3 ± 5.3) using enflurane and a narcotic. In both groups 1 and 2 the fast frequency respiration was studied first in half the patients and in half a slow frequency was studied first. Differences within each group were evaluated using each patient as his own control. Statistical tests appropriate for unpaired data were used for comparisons between groups.

In a third group of patients (group 3: n = 6, age = 7.0 ± 4.7 years), measurements were made during mask anesthesia, but only with the rapid shallow pattern of ventilation characteristic of halothane. We assumed the mask fit was air tight when the volumes of inspiration and expiration measured by the pneumotachograph remained equal and steady throughout the measurement. Following these measurements all six members of this group were intubated and included in group 2. Measurements were made as follows (see box for definition of terms).

$V_D$ = total dead space, namely that portion of the tidal volume that does not equilibrate with the pulmonary blood. This includes anatomical, alveolar, and essential apparatus dead space. It was measured by the following version of the Bohr equation.[4]

$$V_D = \frac{V_T(Pa_{CO_2} - P\bar{E}_{CO_2})}{Pa_{CO_2}} - \text{experimental apparatus}$$

Experimental apparatus = the extra apparatus used in this study which is not routinely used during anesthesia (i.e., Sierra valve and pneumotachograph). This volume was determined by water displacement.

Since not all components of total dead space may respond the same way to changes in frequency and/or tidal volume, wherever possible essential apparatus ($V_{D_{APP}}$) and intrapulmonary ($V_{D_{ST}}$) components were calculated separately as follows.

$V_{D_{APP}}$ was measured by water displacement. It included the appropriately sized endotracheal tube with its standard connector plus 2 ml allotted for connection with an Ayre's T-piece.

$V_{D_{ST}}$ (ml) was obtained by subtracting $V_{D_{APP}}$ from $V_D$. It reflects the intrapulmonary components of dead space distal to the endotracheal tube. It includes contributions from the volume of the conducting airways below the endotracheal tube (residual anatomical dead space), and the alveolar dead space, i.e, alveoli which are either overventilated or underperfused. The apparatus and intrapulmonary components were not separated out during mask anesthesia because the functional dead space volume of a mask is impossible to measure accurately.

Timed, in-phase collections of the arterial blood and expired gases were obtained in duplicate at several intervals throughout the surgical procedure. No collections were made until at least 20 minutes after induction to assure steady-state levels of alveolar nitrous oxide. Arterial blood drawn over a period of 1 minute was stored on ice, analyzed in duplicate for pH, $P_{CO_2}$, and $P_{O_2}$ on a blood gas electrode system (Corning Blood Gas Electrode System) and corrected to patient temperature. These electrodes were calibrated using two known gas mixtures prior to the analysis of each blood sample. With this method the standard deviation for serial measurements of the arterial $CO_2$ tension on a single sample was 0.7 torr. Blood gas correction factors for the electrodes were determined several times daily by tonometry and applied to individual results. Expired gases were collected in a bag and the frequency of ventilation during the 1-minute collection period was recorded. The volumes of the duplicate samples of mixed expired gas were measured with an accurately calibrated syringe (Hamilton syringe) and gas tensions measured with the appropriate electrodes. The standard deviation for multiple measurements of a single gas sample was 0.1 torr. Tidal volumes measured by the syringe were within 5% of the value recorded by the pneumotachograph. All values were corrected to BTPS.

The cumulative error of all these component measurements was evaluated by performing repeated measurements of dead space ($V_{D_{ST}}$) in one patient during steady-state anesthesia with controlled ventilation. Multiple measurements of dead space obtained over a 10-minute period ranged from 28.7 to 30.6 ml with a standard deviation of 0.8 ml.

All values quoted are mean values ± 1 SD. Regression lines were computed using the least squares method.

## Results

### Comparison Among the Three Groups

Mean values of total dead space ($V_D$) expressed as a fraction of the tidal volume are presented in the Table in three groups of patients.

The influence of the type of ventilation can be seen by comparing the $V_D/V_T$ ratio following intubation in eight mechanically ventilated children (group 1) and in 12 children allowed to breathe spontaneously (group 2). Mean frequencies were similar: 30.0 during mechanical ventilation and 35.6 during spontaneous respiration when halothane was utilized to produce a rapid shallow pattern of ventilation. In intubated patients the values for the ratio between total dead space and tidal volume ($V_D/V_T$) of 0.35 ± 0.04 and 0.36 ± 0.04 were not significantly different ( $p > 0.05$). However, during controlled ventilation, tidal volume (expressed as $V_T$/kg) was approximately 50% greater than that observed during spontaneous ventilation in children having a similar age distribution. Since apparatus dead space was similar for the two groups, it follows that the subendotracheal tube or intrapulmonary dead space was larger when ventilation was controlled. The essential apparatus ($V_{D_{APP}}$) contributed a mean of 18.6% of the total dead space during controlled ventilation and 25.0% during spontaneous respiration at these frequencies. These percentages did not vary with age.

The influence of intubation can be seen by comparing groups 2 and 3 when patients spontaneously breathed halothane (Table). The mean $V_D/V_T$ ratio (0.55 ± 0.07) during mask anesthesia (group 3) was significantly higher than that following endotracheal intubation (0.36 ± 0.04) (group 2) ( $p < 0.01$). In six subjects paired measurements were made before and after intubation. In these six, $V_D/V_T$ after intubation was 0.34 ± 0.03; this reflects an average decrease in total dead space of 45% following intubation. The mean arterial carbon dioxide tensions were essentially the same in the two groups (49.0 ± 7.0 torr with a mask and 49.8 ± 6.0 torr following intubation).

### Changes within Group 1

During mechanical ventilation when frequency and tidal volume were varied but $\dot{V}_E$ was kept constant, $V_{D_{ST}}$ increased proportionally with tidal volume in all seven patients (Fig 1A). When the slope of the line for each patient was calculated, the mean value was 0.25 ± 0.05 which was significantly different from 0 ( $p < 0.001$).

**TABLE**

**$V_D/V_T$ with Different Types of Ventilation and Anesthetic Apparatus**

| Group | n | Frequency /min | $V_D/V_T$ | $Pa_{CO_2}$ |
|---|---|---|---|---|
| | | | | *torr* |
| 1. Mechanical-intubated | 8 | 30.0 | 0.35 ± 0.04 | 42.6 ± 5.5 |
| 2. Spontaneous-intubated | 12 | 35.6 ± 9.2 | 0.36 ± 0.04 | 48.5 ± 5.7 |
| 3. Spontaneous-mask | 6 | 29.4 ± 6.9 | 0.55 ± 0.07 | 49.0 ± 7.0 |

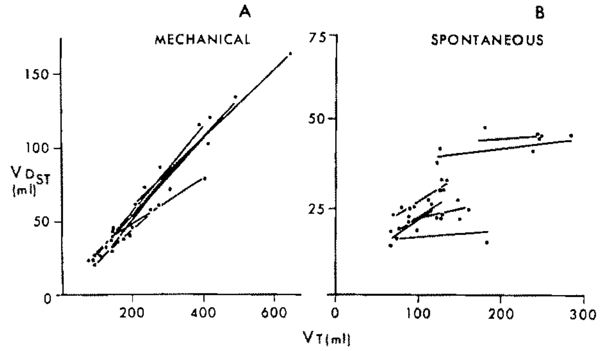


FIG 1. A, Relationship of subendotracheal tube dead space ($V_{D_{ST}}$) to changes in tidal volume ($V_T$) in seven mechanically ventilated patients. $V_{D_{ST}}$ increased in direct proportion to $V_T$ (mean slope 0.25 ± 0.05; $p < 0.001$). B, Response of $V_{D_{ST}}$ to alteration in $V_T$ in seven patients who breathed spontaneously following intubation. For each individual $V_{D_{ST}}$ remained relatively fixed with both small and large tidal volumes. Mean slope of 0.09 ± 0.09 is not significantly different from zero.

When frequency was decreased 67%, from 30 to 10 breaths per minute $V_{D_{ST}}/V_T$ did not change (Fig 2A). The slope of the single dashed line (0 ± 0.001) is the arithmetic mean of the slopes of the seven lines describing the individual responses of $V_{D_{ST}}/V_T$ to frequency changes.[5] It is drawn through the mean value of $V_{D_{ST}}/V_T$ at frequency 30 (0.28 ± 0.03) and demonstrates that there was no change in $V_{D_{ST}}/V_T$ with a 50% decrease in frequency. When the fixed value of anesthetic apparatus was included there was a small but significant decline in $V_D/V_T$ when frequency changed from 30•to 10 (Fig 2B). The dashed line, again an average of the seven individual responses, was drawn through the mean $V_D/V_T$ at frequency 30, and had a significant slope (0.001 ± 0.001) ( $p < 0.025$). These data demonstrate a 15% decrease in $V_D/V_T$ ratio for a 50% decrease in frequency.

### Changes within Group 2

During spontaneous ventilation following intubation the respiratory pattern of seven of the 12 patients was deliberately altered using anesthetic agents. In these children subendotracheal tube dead space did not change with alterations in tidal volume (Fig 1B) as indicated by a mean slope for these seven patients of 0.09 ± 0.09, a slope which is not significantly different from 0 but which is significantly different from the mean slope of the seven patients in group 1 (Fig 1A) who were mechanically ventilated ( $p < 0.001$).

The alterations in $V_{D_{ST}}/V_T$ in response to changes in frequency in seven individual subjects are plotted in Fig 3A both individually and as a single mean (dashed) line with its slope equal to the average of the seven individual slopes (0.002 ± 0.0004). This slope is significantly different from the 0 slope obtained during mechanical ventilation ( $p < 0.001$). It is drawn through the mean $V_{D_{ST}}/V_T$ (0.27 ± 0.04) observed during rapid shallow ventilation (plotted at 0% change) and demonstrates that with spontaneous respiration the $V_{D_{ST}}/V_T$ fell 38% when frequency decreased by 50%. If anesthetic apparatus is included in the measurement of dead space for these seven individuals (Fig 3B) the line representing the mean change of $V_D/V_T$ with change in frequency becomes steeper (slope = 0.003 ± 0.0004) and again is significantly different in slope from the relationship observed during mechanical ventilation that is shown in Fig 2B ( $p < 0.001$). Therefore, during spontaneous ventilation a 50% decline in frequency resulted in a 41% decrease in $V_D/V_T$.

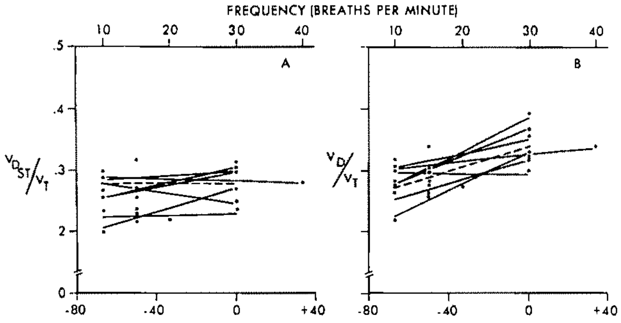


FIG 2. A, Relationship of $V_{D_{ST}}/V_T$ to respiratory frequency in seven patients ventilated mechanically at rates of 10 to 40 breaths per minute. Respiratory rate is expressed both as breaths per minute and as a percent change in frequency from a reference rate of 30. Dashed line has a slope of 0 ± 0.001 which is the mean of the slopes of the seven individual relationships and is drawn through the mean value for $V_{D_{ST}}/V_T$ at a frequency of 30. $V_{D_{ST}}/V_T$ demonstrates no dependence on respiratory rate and therefore tidal volume with mechanical ventilation. B, Relationship of $V_D/V_T$ to frequency in the same group of patients. In this case the mean dashed line has a shallow slope of 0.001 ± 0.001 ($p < 0.025$) that reflects the increased contribution of apparatus dead space to total dead space as frequency increases.

## Influence of Time

Repeated measurements of dead space were made at different times throughout the surgical procedure in six patients from group 1 using identical ventilator settings for I:E ratio, for frequency, and for tidal volume (Fig 4). Four patients showed no change in dead space over a period of 1 to 2 hours of the surgical procedure in two patients dead space increased with time.

Blood pressure and heart rate measured during both controlled and spontaneous ventilation did not change when respiratory pattern was altered.

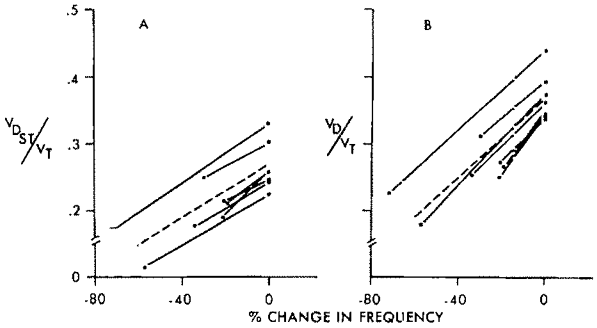


FIG 3. A, Relationship of $V_{D_{ST}}/V_T$ to frequency in the seven spontaneously breathing subjects shown in Fig. 1B. The fastest spontaneous frequency obtained was used as the reference frequency for calculation of percent change. All other respiratory rates are referenced to that value. Dashed line has a slope of 0.002 ± 0.0004 ($p < 0.001$) which is the mean of the seven individual slopes. It is drawn through the mean $V_{D_{ST}}/V_T$ at the reference frequency and demonstrates a 38% fall in $V_{D_{ST}}/V_T$ for a 50% decrease in respiratory rate. B, Relationship of $V_D/V_T$ to frequency in the same group of patients. Mean slope now is 0.003 ± 0.0004 (slope different from that of Fig. 2B at 0.001 level). This relationship predicts a 41% fall in $V_D/V_T$ for a 50% decrease in frequency in spontaneously breathing patients.

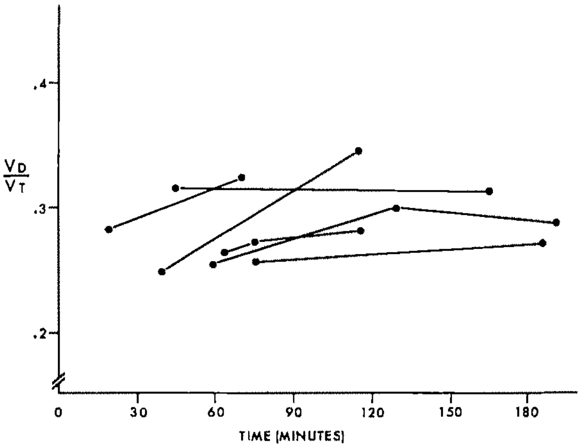


FIG 4. Influence of duration of anesthesia on $V_D/V_T$ in six patients. There was no consistent change when measurements were made under identical conditions of mechanical ventilation and when fluid maintenance and replacement therapy were carefully regulated.

### Relationship to Age

In this study the ratio of dead space to tidal volume showed no variation with age over a range of 1 to 17 years, during either mechanical ventilation at a rate of 15/min or spontaneous ventilation at slow and fast frequencies (Fig 5).

However, when the dead space volume itself was expressed in milliliters per kilogram and related to age a significant relationship became evident (Fig 6). During mechanical ventilation the dead space volume (ml/kg) varied both with frequency and age. For any given age, $V_D$ was larger at lower frequencies (i.e., larger tidal volumes). For any given frequency, $V_D$ decreased with age. At a frequency of 30, $V_D$/kg was 2.78 − (0.1) (age in years) ml ($n = 7$; $r = 0.80$). At a frequency of 10 it increased to 6.74 − (0.25) (age in years) ml ($n = 7$; $r = 0.73$) (Fig 6B). During spontaneous ventilation following intubation the dead space volumes were smaller and showed no dependence on frequency. $V_D$/kg was 1.72 − (0.06) (age in years) ml ($n = 12$; $r = 0.82$) at mean frequency of (fast) 35.6, and $V_D$/kg was 1.93 − (0.06) (age in years) ml ($n = 7$; $r = 0.73$) at mean frequency of 23.2 (slow) (Fig 6A).

## Discussion

### Influence of Type and Pattern of Ventilation

Nunn and Hill[1] concluded that the respiratory system was somewhat protected from the dangers of hypo- and hyperventilation because dead space readjusted itself appropriately to changes in tidal volume to maintain a constant ratio of dead space and tidal volume. Our study confirms this concept only during controlled ventilation. When we tripled tidal volume, using a mechanical respirator, the ratio of the total dead space and tidal volume remained for practical purposes essentially constant. However, with spontaneous ventilation the breathing pattern exerted a strong influence such that a constant relationship of dead space and tidal volume no longer existed. Instead both subendotracheal tube and apparatus dead space volumes remained fixed, despite wide variations in tidal volume. This indicates that when a spontaneously breathing patient increases his tidal volume, the increased gas flow is appropriately distributed to well

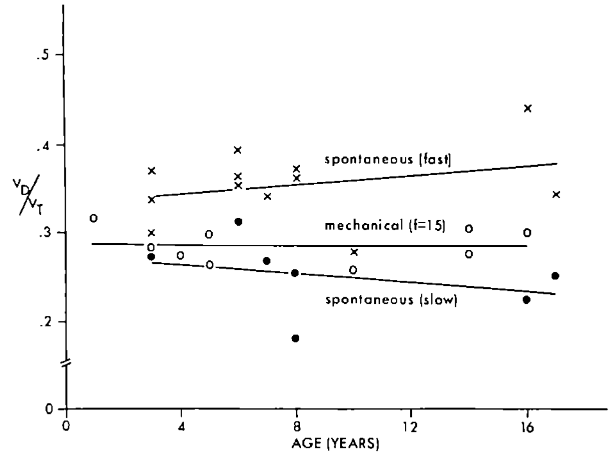


FIG 5. Relationship of age (in years) to $V_D/V_T$ in mechanically ventilated patients ($f = 15$) and spontaneously breathing patients (both fast and slow). None of these lines has a slope significantly different from zero, demonstrating that $V_D/V_T$ ratio bears no relationship to age in healthy children aged 1 to 17 years.

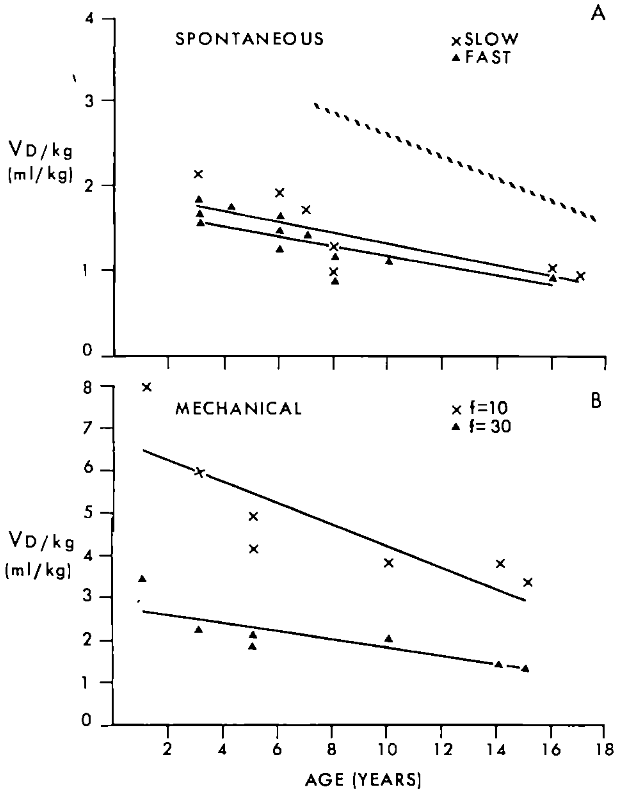


FIG 6. A, Relationship between total dead space ($V_D$) in milliliters per kilogram and age in intubated spontaneously breathing anesthetized children. $V_D$/kg = 1.93 − (0.06) (age in years) ml at $f = 23.2 \pm 5.4$ ($n = 7$; $r = 0.73$; $p < 0.05$). $V_D$/kg = 1.72 − (0.06) (age in years) ml at $f = 35.6 \pm 9.2$ ($n = 12$; $r = 0.82$; $p < 0.01$). The decrease in $V_D$/kg with increasing age is identical with both slow and rapid respirations. Broken line was calculated from Levison's data for awake children breathing through a mouthpiece[18] $V_D$/kg = 3.91 − (0.13) (age in years) ml. B, Relationship between dead space ($V_D$/kg) and age during slow and fast rates of mechanical ventilation. The wasted ventilation was always greater than that measured during spontaneous ventilation under anesthesia (A) and was significantly affected by respiratory rate. $V_D$/kg = 6.74 − (0.25) (age in years) ml at $f = 10$ ($n = 7$, $r = 0.83$, $p < 0.05$). $V_D$/kg = 2.78 − (0.10) (age in years) ml at $f = 30$ ($n = 7$, $r = 0.80$, $p < 0.05$).

perfused areas of the lung. The result is a significant change in the ratio of the total dead space to tidal volume with alterations in frequency and tidal volume. A rapid shallow respiratory pattern is associated with a high $V_D/V_T$ ratio, but a slow deep pattern of ventilation is effective in reducing this ratio.

With controlled ventilation (Fig 1A) the subendotracheal tube dead space adjusts in direct proportion to changes in tidal volume. Furthermore, when one calculates the total dead space (in ml/kg of body weight) and relates it to the age of each individual studied, the volume of the wasted ventilation during positive pressure breathing is found to exceed that observed during spontaneous respiration no matter what respiratory pattern is used (Fig 6). This result in children agrees with previous studies in dogs[6] and adults,[7] where the dead space volume during controlled ventilation was larger than the volume during spontaneous ventilation with an identical tidal volume. This increase in the overventilated volume of the lung could reflect alterations in the distribution of either ventilation or perfusion induced by the use of controlled respiration. A shift in ventilation distribution away from dependent well perfused zones and toward nondependent poorly perfused lung regions during paralysis and mechanical ventilation has been demonstrated both by Froese and Bryan[8] using a radiographic technique and by Rehder et al[9] using the analysis of nitrogen clearance curves. In addition the distribution of pulmonary blood flow depends strongly on the relationship between pulmonary artery pressure and intra-alveolar pressure.[10] The delivery of a larger tidal volume by positive pressure ventilation requires an increase in intra-alveolar pressure which alters this balance of pressures. A resultant decrease in pulmonary perfusion in some lung regions could therefore also account for the observed increase in dead space through an increase in the alveolar component. A further factor was demonstrated by Hedenstierna and McCarthy[11] who found that an increase in tidal volume during controlled ventilation enlarged the volume of the conducting airways. All of these mechanisms could explain the changes demonstrated in this study.

In this study the apparatus contributed to a small but statistically significant increase in the ratio between total dead space and tidal volume as frequency increased which would be of minimal physiologic significance. Therefore if one were to assume $V_D/V_T$ to be constant during controlled ventilation the resultant errors in gas exchange calculations would be small and clinically unimportant over a wide range of frequencies. However, it must be stressed that this conclusion applies only when the volume of apparatus dead space is comparable to that used in this study (10.0% of total dead space at a frequency of 10 or 18.6% at a frequency of 30). If the apparatus dead space were to be increased, then the frequency dependence of the $V_D/V_T$ ratio would be accentuated and could well reach physiologic significance.

Our data appear to be at variance with that of Nunn and Hill.[1] They measured the $V_{D_{ST}}/V_T$ ratio once in each of 12 adults breathing spontaneously, with an unselected pattern of ventilation. Their mean value, 0.32 exhibited a wide standard deviation with results varying from 0.09 to 0.41. This range includes all values of $V_{D_{ST}}/V_T$ observed in our study, no matter what the pattern of ventilation. Their experimental design did not allow them to examine intraindividual influences of respiratory pattern on dead space. However, from our study it becomes evident that large variations in the $V_{D_{ST}}/V_T$ ratio occur with changes in frequency and tidal volume within individuals, whereas variations between individuals with similar respiratory patterns are small (observed standard deviation in this study 0.04).

This last observation makes it unlikely that our conclusions were materially affected by our inability to use a single, homogeneous population throughout all measurements. Although it would have been ideal to make measurements in a single group of patients at all frequencies during both modes of ventilation, we were limited by time and often by the nature of the surgical procedure. However, in two patients $V_D/V_T$ was measured during both spontaneous and controlled ventilation although not over the entire range of frequencies. These single measurements of $V_D/V_T$, one during spontaneous ventilation at a rapid frequency and the other during controlled ventilation at a frequency of 30, both fell within the variance of the larger experimental groups.

A reduction in dead space with a decrease in tidal volume during spontaneous ventilation is not totally unlikely; Briscoe et al[12] demonstrated that fresh gas can penetrate into alveoli even when respirations are smaller than the estimated volume of the conducting airways. They attributed this phenomenon to the effect of cardiogenic oscillations and the greater streamlining of laminar flow with small tidal volumes. These two mechanisms could explain the observed tendency for dead space to decrease with the smaller tidal volumes in all of our spontaneously breathing patients (Fig 1A). However, during anesthesia these factors were not sufficient to keep $V_D/V_T$ constant.

Although a variety of pharmacologic agents was used in this study, it is unlikely that this influenced the conclusions. Atropine, an agent known to inhibit changes in bronchomotor tone, was administered to all patients within 2 hours prior to the measurement of dead space.[13] Little difference has been shown in the bronchodilating properties of halothane and enflurane.[14] An inspired oxygen concentration of 50% was used in all cases to avoid the effect of changes in inspired oxygen tension on airway diameter.[15]

This study demonstrates that during spontaneous ventilation the fraction of wasted ventilation was less with a large tidal volume than with a small tidal volume. Although arterial $CO_2$ tensions were measured in these patients and did in fact show more effective $CO_2$ elimination with the slow deep pattern of respiration, it would be dangerous to place much weight on that data since no effort was made to guarantee the use of equivalent depths of anesthesia with the two different techniques. The more efficient pattern of ventilation in this study was achieved using enflurane plus narcotics, but one must be cautious in recommending this combination since both are potent respiratory depressants.[16, 17] This danger was avoided in our patients by careful titration with a continuous recording of frequency and tidal volume. Therefore, an ideal anesthetic agent should be associated with both a large tidal volume and a minimal degree of respiratory depression.

### Influence of Time

Askrog et al[18] demonstrated a progressive increase in dead space with duration of anesthesia, but they made no mention of fluid management. In our study, fluid replacement was carefully controlled and no such relationship could be demonstrated (Fig 4). Therefore, we question whether the observations of Askrog et al simply reflected a cumulative fluid deficit which only coincidentally related to the duration of anesthesia.

### Influence of Anesthesia

Our values obtained during anesthesia with various patterns of respiration are compared with measurements obtained by Levison et al[19] in awake supine children (Fig 6A). As stated before, there is essentially no difference in total dead space whether one chooses a fast or slow spontaneous respiratory rate. The dead space with spontaneous ventilation following endotracheal intubation is approximately one half that calculated from Levison's data in awake unintubated children. Since calculations from several studies[20] suggest that endotracheal intubation decreases dead space by approximately 50%, the intrapulmonary dead space would appear to be very similar in awake and anesthetized spontaneously breathing children.

### Influence of Age

The mean values for the $V_{D_{ST}}/V_T$ ratios in this study of children following intubation (0.28 ± 0.03 during controlled and 0.27 ± 0.04 during spontaneous respiration with halothane anesthesia) are similar to measurements reported in adults by Hedenstierna and McCarthy[11] ($V_{D_{ST}}/V_T$ 0.25 during controlled ventilation) and by Nunn and Hill[1] (0.32 during both controlled and spontaneous respiration). Similarly, the study of Kain et al[21] of adults breathing spontaneously with a mask demonstrated a high $V_D/V_T$ ratio similar to the value obtained in our study. The occurrence of such similar values in studies spanning infancy to middle age is further evidence that $V_D/V_T$ ratio is independent of age. However, this is not the case with the actual volume of dead space. Dead space volume per kilogram consistently decreases with increasing age over a range of one to 17 years and depends on the type of ventilation. With controlled ventilation it also depends on the rate of respiration (Fig 6). Therefore, the usual convenient approximation of 1 ml of dead space per pound of body weight suggested for adults[22] leads to significant errors in the estimation of dead space in children.

It may appear rather arbitrary to relate $V_D/V_T$ and $V_{D_{ST}}/V_T$ to percent decrease in frequency in spontaneously breathing patients. However, this was necessary because of the well known variation of respiratory frequency with age.[22, 23] A 2 year old typically breathes at a rate of 45 under halothane anesthesia, the 16 year old at a rate of 20. However, both have similar $V_D/V_T$ ratios (Fig 5) at these 'usual' frequencies. Plotting the data in the present way emphasizes that any given patient, starting at his usual breathing frequency, would substantially decrease his fraction of wasted ventilation if a slower, deeper pattern of respiration could be induced without depressing his minute ventilation.

The concept that dead space adjusts to changes in tidal volume such that the $V_D/V_T$ ratio remains a constant makes for convenient calculations. This assumption has been adopted in many gas exchange equations. However, it is evident from our data that such an assumption is incorrect. There is definitely a penalty for breathing at high respiratory rates and low tidal volumes. With mechanical ventilation the changes in $V_D/V_T$ ratio with alterations in pattern are small and physiologically insignificant. The important feature is that the dead space is larger at any frequency compared with values during spontaneous respiration. However, during spontaneous breathing changes in pattern have a definite impact. A rapid shallow pattern is associated with high $V_D/V_T$ ratios; with a low frequency and large tidal volume the ratio drops markedly. This indicates that only during spontaneous respiration is an increase in tidal volume appropriately matched to perfusion to facilitate efficient gas exchange.

## ACKNOWLEDGMENTS

The authors acknowledge with appreciation the assistance of Mr. George Volgyesi, Dr. A. C. Bryan, and the members of the Department of Anesthesia, Hospital for Sick Children, Toronto, throughout this study.

## REFERENCES

1. Nunn JF, Hill DW: Respiratory dead space and arterial to end-tidal $CO_2$ tension difference in anesthetized man. J Appl Physiol 15:383–389, 1960
2. Severinghaus JW, Stupfel M: Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries. J Appl Physiol 10:335–348, 1957
3. Volgyesi G, Nisbet HJA: A new piston ventilator for use in respiratory studies. Can Anaesth Soc J 19:662, 1972
4. Nunn JF: Applied Respiratory Physiology, with Special Reference to Anaesthesia. First edition. London, Butterworths, 1969, p 191
5. Regan MJ, Eger EI II: Ventilatory responses to hypercapnia and hypoxia at normothermia and moderate hypothermia during constant-depth halothane anesthesia. Anesthesiology 27:624–633, 1966
6. Suwa K, Hedley-Whyte J, Bendixen HH: Circulation and physiological dead space changes on controlling the ventilation of dogs. J Appl Physiol 21:1855–1859, 1966
7. Campbell EJM, Nunn JF, Peckett BW: A comparison of artificial ventilation and spontaneous respiration with particular reference to ventilation-blood flow relationships. Br J Anaesth 30: 166–175 1958
8. Froese AB, Bryan AC: Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242–255, 1974
9. Rehder K, Hatch DJ, Sessler AD, et al: Effects of general anesthesia, muscle paralysis and mechanical ventilation on pulmonary nitrogen clearance. Anesthesiology 35:591–601, 1971
10. West JB Respiratory Physiology—The Essentials. First edition. Baltimore, Williams & Wilkins Co., 1975, pp 39–41
11. Hedenstierna G, McCarthy G: The effect of anaesthesia and intermittent positive pressure ventilation with different frequencies on the anatomical and alveolar deadspace. Br J Anaesth 47:847–852, 1975
12. Briscoe WA, Forster RE, Comroe JH Jr: Alveolar ventilation at very low tidal volumes. J Appl Physiol 7:27–30, 1954
13. Sullivan CE, Zamel N, Kozar LF, et al: Regulation of airway smooth muscle tone in sleeping dogs. Am Rev Respir Dis 119: 87–99, 1979
14. Morr-Strathmann U, Welter J, Lawin P: Die Beeinflussung physiologischer Atemgrössen durch Ethrane und Halothan (English abstract). Anaesthesist 26:165–167, 1977
15. Sykes MK, Finlay WEI: Dead space during anaesthesia—effect of added oxygen. Anaesthesia 26:22–27, 1971
16. Wolfson B, Hetrick WD, Lake CL, et al: Anesthetic indices—further data. Anesthesiology 48:187–190, 1978
17. Foldes FF, Swerdlow M, Siker ES: Narcotics and Narcotic Antagonists. First edition. Springfield, IL, Charles C Thomas, 1964, p 49
18. Askrog VF, Pender JW, Smith TC, et al: Changes in respiratory dead space during halothane, cyclopropane and nitrous oxide anesthesia. Anesthesiology 25:342–352, 1964
19. Levison H, Featherby EA, Weng TR: Arterial blood gases, alveolar-arterial oxygen difference and physiological dead space in children and young adults. Am Rev Respir Dis 101: 972–974, 1970
20. Nunn JF, Campbell EJM, Peckett BW: Anatomical subdivisions of the volume of respiratory dead space and effect of position of the jaw. J Appl Physiol 14:174–176, 1959
21. Kain ML, Panday J, Nunn JF: The effect of intubation on the dead space during halothane anaesthesia. Br J Anaesth 41:94–101, 1969
22. Radford EP: Ventilation standards for use in artificial respiration. J Appl Physiol 7:451–459, 1955
23. Wilson LA, Harrison GA: Pulmonary ventilation in children during halothane anesthesia. Anesthesiology 25:613–619, 1964

ANESTH ANALG
59:350-354, 1980

# Bronchofiberscopic Jet Ventilation

**Tanguturi Satyanarayana, MD,* Levon Capan, MD,† Sivam Ramanathan, MD,‡ Jack Chalon, MD,§ and Herman Turndorf, MD‖**

SATYANARAYANA, T., CAPAN, L., RAMANATHAN, S., CHALON, J., AND TURNDORF, H.: Bronchofiberscopic jet ventilation. Anesth Analg 59: 350–354, 1980.

The suction-biopsy channel of a flexible bronchofiberscope was used to provide subglottic jet ventilation in six dogs and eight adult human subjects. In dogs, after 75 minutes of ventilation at a driving pressure of 2580 torr/cm$^2$ (50 lb/in$^2$) the $Pa_{O_2}$ was 412 ± 18 torr and the $Pa_{CO_2}$ 32 ± 3 torr with a peak airway pressure of 6 torr. In patients, after 30 minutes of jet ventilation, the $Pa_{O_2}$ varied from 347 to 480 torr, the $Pa_{CO_2}$ from 17 to 36 torr, and peak tracheal pressure from 6 to 8 torr. The method is convenient, simple and applicable in a variety of clinical situations.

**Key Words:** VENTILATION, Jet; EQUIPMENT, Bronchofiberscope.

THE TECHNIQUE of jet ventilation consists of lung inflation by a high pressure gas source delivered intermittently into the trachea through either a transtracheal or an orotracheal cannula.[1] The method has been advocated for the anesthetic management of endolaryngeal surgery[2] and rigid[3] and flexible bronchoscopy,[4] and it has been advocated to provide emergency ventilation during cardiac resuscitation.[5] We have used the suction-biopsy channel of a flexible fiberoptic bronchoscope to deliver jet ventilation and found that it produced adequate pulmonary gas exchange for prolonged periods of time.

## Methodology

### Animal Experiments

Five dogs weighing between 18 to 22 kg each were anesthetized by continuous intravenous infusion of thiopental. A femoral artery was cannulated for measurement of blood gas tensions and arterial pressure. A flexible fiberoptic bronchoscope (American Cystoscope, model FO 8800-D) with a suction-biopsy channel 68 cm long and 2 mm i.d., was introduced 6 cm beyond the vocal cords. The Luer fitting of the suction-biopsy port was connected to a Sander's ventilating system (Pitting Company, Washington, PA) and used to provide jet ventilation (Fig 1). The additional opening of the port was closed by a three-way stop-cock. The injection system consisted of a toggle release valve attached to a single-stage pressure regulator (Fig 1). Tracheal pressure was monitored by a no. 14 suction catheter introduced alongside the bronchoscope. The catheter tip was 4 cm below the tip of the vocal cords and its free end attached to a transducer. Jet ventilation was provided by manual compression of the toggle switch for approximately 1 second, 18 to 20 times per minute, at a driving pressure of 2580 torr/cm$^2$ (50 lb/in$^2$). The chest was bilaterally inflated as was determined by auscultation. Arterial blood samples were obtained 3, 10, 15, 30, 60, and 75 minutes after the start of experiments. A second suction catheter was passed (at the end of 75 minutes) into the trachea 4 cm beyond the vocal cords and its free end connected in series, both to an oxygen analyzer and a capnograph. The capnograph pump was set at 0.5 L/min for six or seven inflations and tracheal oxygen and $CO_2$ concentrations were measured. In addition, a 6-mm i.d. cuffed endotracheal tube was inserted alongside the bronchoscope and the suction catheters. The open end of the endotracheal tube was connected to the expiratory limb of a Collin's spirometer fitted with a unidirectional valve. This

---

* Resident.
† Associate Clinical Professor.
‡ Associate Professor.
§ Professor.
‖ Professor and Chairman.

Received from the Department of Anesthesiology, New York University Medical Center, H-623, 550 First Avenue, New York, New York 10016. Accepted for publication January 16, 1980.

Reprint requests to Dr. Ramanathan.

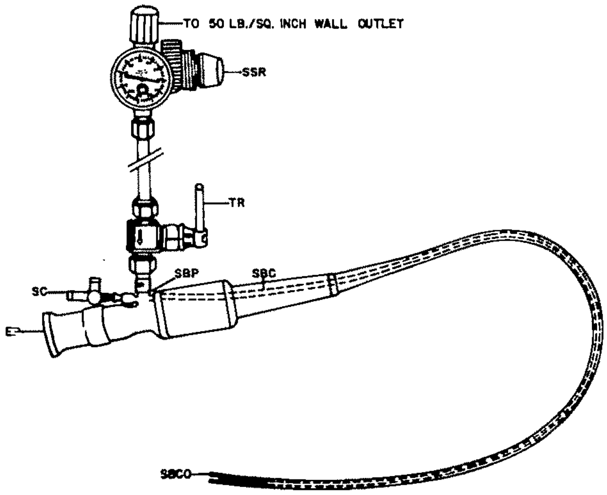


FIG 1. Bronchofiberscopic jet ventilation system. SSR, Single stage regulator; TR, toggle release switch; SC, stop-cock closing off the additional outlet; SBP, suction-biopsy channel; EP, eye piece; SBCO, suction-biopsy channel outlet.

prevented gas entrainment from the spirometer to the trachea, due to a Venturi effect. The spirometer drum rotated from left to right at a speed of 160 mm/min. Expiratory tidal volume was measured over 10 respiratory cycles. The endotracheal tube and the gas sampling catheters were then removed, and the animals were allowed to recover from anesthesia. Experiments were repeated at pressures of 2067 and 1550 torr/cm$^2$. Results were expressed as the mean (± 1 SD) of five measurements for each injection pressure.

An additional dog weighing 20 kg was studied as follows: The tip of the suction catheter was placed successively at the following sites: (1) at the level of the vocal cords, (2) 2 cm above the tip of the bronchoscope, and (3) 1.5 cm below the tip of the instrument. Pressure recordings were made at 2580 torr jet ventilation. Tidal volume was measured by the method outlined above. The bronchoscope and the endotracheal tube (used to measure tidal volume) were removed and the trachea intubated with an 8.5-mm i.d. cuffed endotracheal tube. The animal was ventilated by an Airshields ventimeter/ventilator on a conventional circle absorber system at the tidal volume measured during jet ventilation, a rate of 20/min and a fresh gas inflow (FGI) of 4 L/min. Airway pressure was recorded through the suction catheter with its tip 4 cm below the vocal cords. The entire experiment was repeated three times to assess reproducibility of findings.

### Clinical Study

Informed consent was obtained from eight adult patients aged 20 to 40 years. All were free from cardiopulmonary disease. They were scheduled for gynecologic procedures and received 0.4 mg of atropine and 50 mg of meperidine 45 minutes prior to induction of anesthesia. An arterial line was placed using local anesthesia. Anesthesia was induced with thiopental (250 mg) followed by succinylcholine (100 mg). The fiberoptic bronchoscope was introduced through the nose into the trachea 6 cm below the vocal cords. Airway pressure was monitored by a suction catheter as previously described. Anesthesia was maintained by continuous infusions of 0.1% methohexital and 0.2% succinylcholine. Jet ventilation was provided by the same system as was used in dogs with a driving pressure of 2580 torr/cm$^2$ at a frequency of 18 to 20 times per minute. Tracheal $O_2$ concentration was monitored by aspirating gas samples from the catheter over 20 respiratory cycles. Arterial gas tensions were measured before induction and 3 and 30 minutes after the start of jet ventilation.

## Results

### Animal Experiments

In the animal study arterial oxygenation and $CO_2$ elimination were adequate during 75 minutes of 2580 torr jet ventilation (Table 1). Peak airway pressure was 6 torr and tracheal $CO_2$ concentration oscillated between 0.4% during jet flow and 2% during the postexpiratory pause (Fig 2) (Table 2). Tracheal oxygen concentration was 90 ± 2% and tidal volume 475 ± 18 ml. When the driving pressure was reduced, tidal volume, $Pa_{O_2}$ and airway pressure decreased and $Pa_{CO_2}$ increased (Table 2). Tracheal oxygen concentration did not vary significantly with different driving pressures (Table 2).

**TABLE 1**

**Dog Study of Arterial Blood Gas Tensions and Tracheal Peak Pressures***

| Time | Arterial pH | $Pa_{CO_2}$ | $Pa_{O_2}$ | Peak tracheal pressure |
|---|---|---|---|---|
| *min* | | *mm Hg* | *mm Hg* | *torr* |
| 2 | 7.40 ± 0.02 | 36 ± 4 | 389 ± 17 | 6 |
| 10 | 7.42 ± 0.03 | 29 ± 3 | 392 ± 29 | 6 |
| 15 | 7.43 ± 0.02 | 29 ± 4 | 430 ± 20 | 6 |
| 30 | 7.44 ± 0.02 | 28 ± 4 | 420 ± 20 | 6 |
| 60 | 7.43 ± 0.02 | 29 ± 4 | 418 ± 21 | 6 |
| 75 | 7.43 ± 0.02 | 32 ± 3 | 412 ± 18 | 6 |

* Values are means of five observations ± 1 SD at various times during jet ventilation through the suction-biopsy channel of the flexible bronchofiberscope at a driving pressure of 2580 torr/cm$^2$ at a frequency of 18 to 20 times per minute.

Pressure recordings at the level of the vocal cords exhibited two distinct phases of equal durations (Fig 3, A) during jet inspiration. The first phase was negative (approximately −3 torr) and the second phase always positive (4.5 torr). Peak pressures at points 2 cm above and 1.5 cm below the tip of the bronchoscope (Fig 3, B and C) were both 6 ± 0 torr. Conventional endotracheal intermittent positive pressure respiration (IPPR) produced a peak pressure approximately double that produced by 2580 torr jet ventilation (Fig 4).

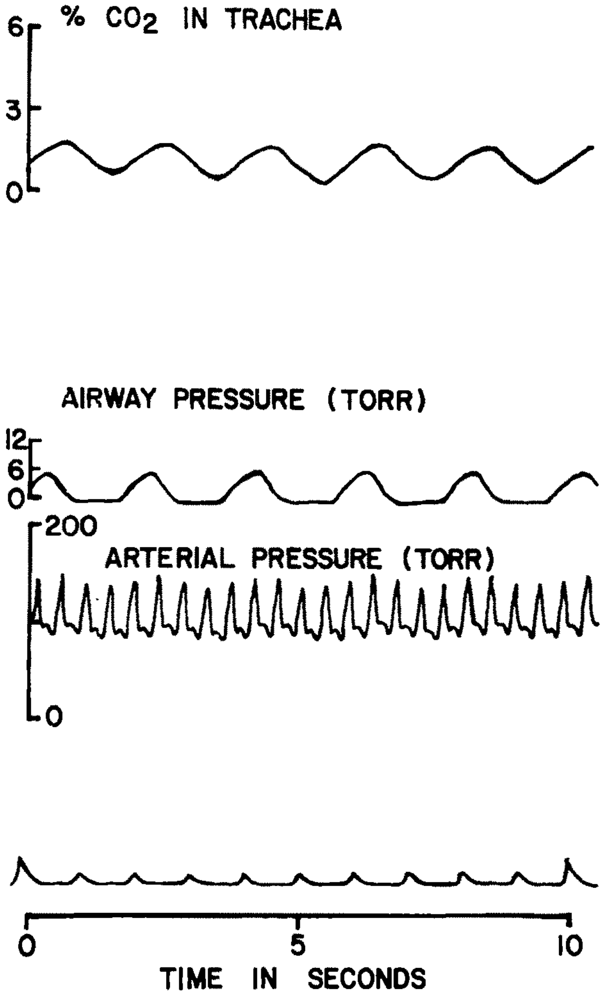


Fig 2. Polygraph recording of tracheal $CO_2$ concentration, tracheal pressures, and arterial blood pressure during jet ventilation of dogs through the suction-biopsy channel of the flexible bronchoscope at a driving pressure of 2580 torr/cm$^2$ (50 lb/in$^2$) at a frequency of 18 to 20 times per minute.

## Clinical Study

Under clinical conditions (Table 3) good arterial oxygenation and moderate to severe hypocarbia were

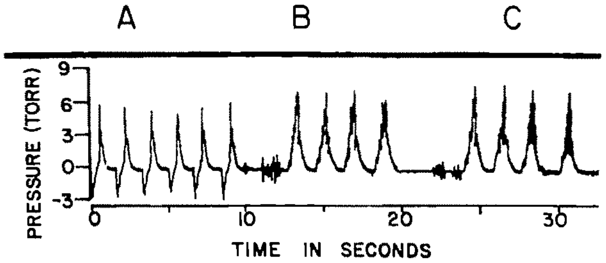


Fig 3. Canine airway pressure recording during 2580 torr jet ventilation (respiratory rate approximately 25/min): A, pressure changes at the level of the vocal cords; B, 2 cm above the tip of the bronchoscope; C, 1.5 cm below the tip of the bronchoscope. In A, the pressure is subatmospheric during the initial phase of injection and positive in the late phase.

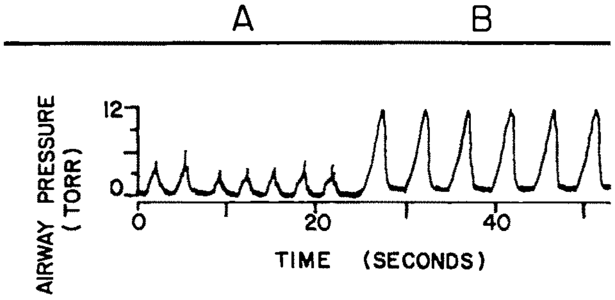


Fig 4. Comparison between canine airway pressure during jet ventilation (A: driving pressure 2580 torr/cm$^2$, rate 25/min) and conventional endotracheal intermittent positive pressure respiration (B: tidal volume 475 ml, fresh gas inflow 4 L/min, rate 20/min). Note that IPPR inflation pressure (11.5 torr) is approximately double that seen with jet ventilation (6 torr).

**TABLE 2**

**Dog Study of Tracheal Oxygen Concentration, Oscillations in $CO_2$, Peak Pressures, Arterial Blood Gas Tensions, and Tidal Volumes***

| Driving pressure | Tracheal $O_2$ concentration | Mean tracheal $CO_2$ oscillations | Tidal vol | Arterial pH | $Pa_{CO_2}$ | $Pa_{O_2}$ | Peak airway pressure |
|---|---|---|---|---|---|---|---|
| *torr/cm$^2$* | *%* | *%* | *ml* | | *mm Hg* | *mm Hg* | *torr* |
| 1550 | 89 ± 2 | 0.4 ± 0 to 4.0 ± 0.2 | 150 ± 15 | 7.26 ± 0.02 | 53 ± 3 | 272 ± 19 | 3.3 ± 0 |
| 2067 | 89 ± 3 | 0.4 ± 0.05 to 2.8 ± 0.1 | 300 ± 16 | 7.38 ± 0.03 | 36 ± 4 | 369 ± 14 | 4.5 ± 0 |
| 2580 | 90 ± 3 | 0.4 ± 0 to 2.0 ± 0.1 | 475 ± 18 | 7.43 ± 0.02 | 32 ± 3 | 412 ± 18 | 6.0 ± 0 |

* Results are means ± 1 SD of five observations after 75 minutes of jet ventilation of dogs through the suction-biopsy channel of flexible bronchofiberscope at a frequency of 18 to 20 times per minute. Lower $CO_2$ concentrations were obtained during jet inflations and the higher concentrations between inflations.

found ($Pa_{O_2}$ 347 to 480 torr and $Pa_{CO_2}$ 16 to 36 torr). Tracheal oxygen concentrations varied between 88% and 92%. No tracheal pressure higher than 8 torr was noted (Fig 5). Postoperative course was uneventful in all cases.

**TABLE 3**

**Clinical Study of Tracheal Oxygen Concentrations, Arterial Blood Gas Tensions, and Peak Tracheal Pressures***

| Patient | Weight | Sampling interval | Tracheal $O_2$ concentration | Arterial pH | $Pa_{CO_2}$ | $Pa_{O_2}$ | Peak airway pressure |
|---|---|---|---|---|---|---|---|
| 1 | 77 | 3 | 92 | 7.44 | 34 | 347 | 7 |
| | | 30 | 93 | 7.47 | 32 | 355 | 7 |
| 2 | 72 | 3 | 88 | 7.49 | 30 | 480 | 8 |
| | | 30 | 89 | 7.50 | 28 | 478 | 8 |
| 3 | 72 | 3 | 89 | 7.48 | 36 | 465 | 7 |
| | | 30 | 90 | 7.49 | 34 | 460 | 7 |
| 4 | 100 | 3 | 92 | 7.53 | 25 | 419 | 8 |
| | | 30 | 91 | 7.57 | 17 | 356 | 8 |
| 5 | 55 | 3 | 88 | 7.42 | 26 | 410 | 7 |
| | | 30 | 90 | 7.46 | 23 | 413 | 7 |
| 6 | 55 | 3 | 89 | 7.47 | 36 | 340 | 6 |
| | | 30 | 91 | 7.55 | 16 | 354 | 6 |
| 7 | 45 | 3 | 91 | 7.51 | 24 | 450 | 8 |
| | | 30 | 88 | 7.51 | 26 | 460 | 8 |
| 8 | 49 | 3 | 92 | 7.54 | 23 | 440 | 7 |
| | | 30 | 89 | 7.52 | 26 | 468 | 7 |

* Patients were ventilated through the suction-biopsy channel of a bronchofiberscope at a frequency of 18 to 20 times per minute. Sampling was performed at 3 and 30 minutes from the start of jet ventilation.

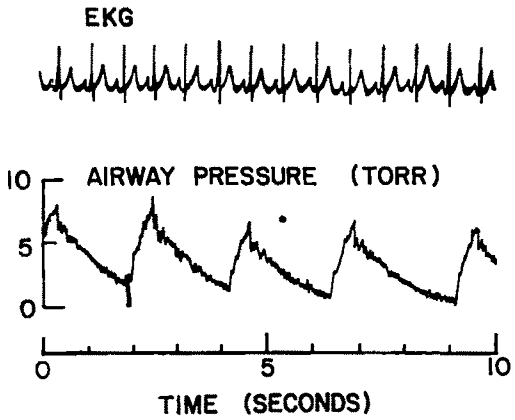


FIG 5. EKG and tracheal pressure recordings of a patient during jet ventilation through the suction-biopsy channel of the flexible bronchoscope at a driving pressure of 2580 torr/cm$^2$ (50 lb/in$^2$), ventilated at a rate of 18 to 20/min. Each vertical line on the abscissa represents 1 second.

## Discussion

When a high pressure gas jet is delivered axially into a diffusor tube, the total outflow is greater than the jet flow (because of air entrainment at the diffusor inlet). Any resistance to outflow from the diffusor will cause the pressure in the system to increase, converting the injector into a positive pressure generator. During jet ventilation the trachea functions as the diffusor and the lungs create the outflow resistance. The subatmospheric pressure that develops in the upper airway during the initial phase of jet inspiration (Fig 3, A) has been said to cause collapse of the periglottic soft tissues.[1] This produces partial airway obstruction, limiting air entrainment during injection.[1] The intratracheal pressure itself, however, is positive during jet flow (Fig 3, B and C). The tracheal pressures recorded 4 and 7.5 cm below the vocal cords are monophasic and reach a peak value of 6 torr in both instances. The positive pressure overcomes the airway obstruction (caused by the negative pressure) and produces a positive deflection of the pressure trace (Fig 3 A). When jet flow ceases, the elastic recoil of the lungs expels injected gases through the open upper airway.

Many studies have attested to the efficacy of jet ventilation through a cricothyroidotomy[1, 5] or through suction catheters inserted in the trachea.[4, 6] Our studies also show that the suction-biopsy channel of the bronchofiberscope can be used as an efficient injector channel to provide sustained pulmonary gas exchange at a driving pressure of 2580 torr/cm$^2$ (50 lb/in$^2$). On the other hand, a 1550 torr/cm$^2$ pressure produces a smaller tidal volume (150 ± 15 ml) and leads to diminished alveolar ventilation and higher $Pa_{CO_2}$ (53 ± 3 torr).

In dogs, peak and mean airway pressures during 2580 torr jet ventilation reached 6 ± 0 torr and 3.5 ± 0 torr with a tidal volume of 475 ml. In patients these pressures were 7.3 ± 0.7 and 4.5 ± 0.3 torr. Peak airway pressure produced by conventional intermittent positive pressure respiration attains approximately twice the peak jet inflation pressure (Fig 4). The lower pressure seen with the injection technique may be due to opening of the upper airway when tracheal pressure exceeds a critical level (relief-valve action). However, during IPPR, the entire tidal volume is delivered into a closed system, causing higher pressures.

The high tracheal oxygen concentrations obtained with jet ventilation suggest minimal air entrainment. In spite of a constant $F_{IO_2}$ lower driving pressures lead to a decrease in $Pa_{O_2}$, probably because of ventilation-perfusion aberrations associated with low tidal volumes. End-tidal $CO_2$ was consistently lower than $Pa_{CO_2}$ at all driving pressures. For instance, with 2580 torr jet ventilation, the mean end-tidal $CO_2$ was 2% (14 torr) and the mean $Pa_{CO_2}$ 31 torr. We cannot adequately explain this disparity. It is known, however, that end-tidal $CO_2$ concentration differs from $Pa_{CO_2}$ by as much as 10 torr during anesthesia.[7] Our findings may have been affected by the same mechanisms.

The endotracheal tube acts as an efficient air entrainment channel and artificially raises tidal volume during jet inflation. Spoerel et al[1] have shown that up to 40% of the tidal volume can be derived from air entering the thorax via the endotracheal tube during jet inspiration. This did not occur in our study because a unidirectional valve, placed at the expiratory limb of the spirometer, closed off the expiratory limb during jet inflation. The tracing in Fig 6 remains horizontal (segment AB) during both the expiratory pause and jet inflation. This indicates the absence of gas exchange between the lungs and the spirometer during these phases. Removal of the valve leads to air entrainment from the system and results in an upward swing of the tracing during jet inflation as in the studies by Spoerel et al.[1] Volume changes in the spirometer (downward displacement of segment BC in Fig 6) are, therefore, only due to exhaled tidal volume.

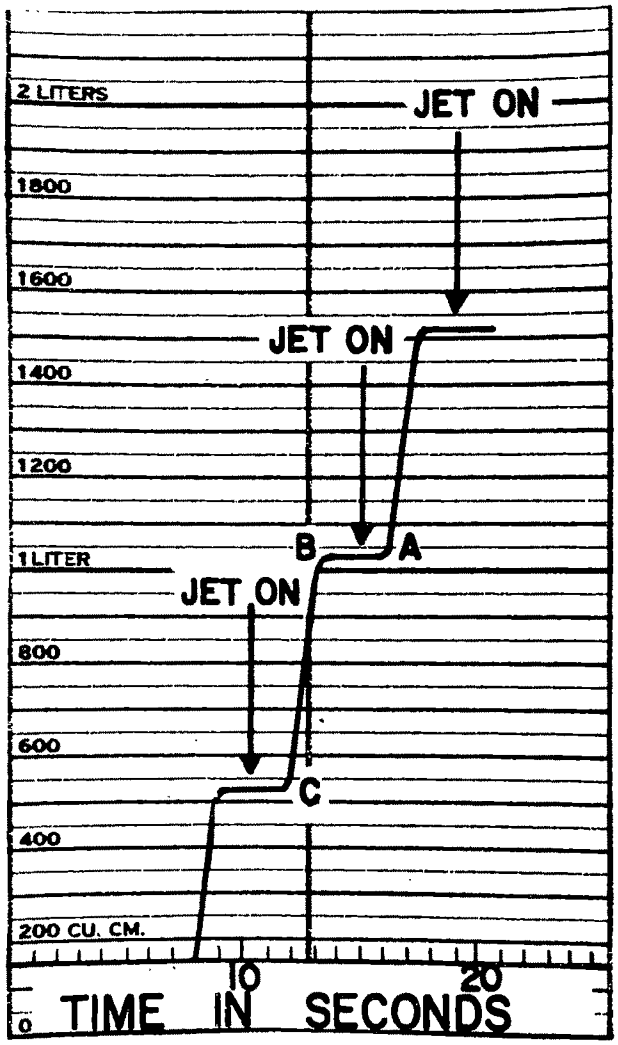


FIG 6. Spirometer tracing during tidal volume measurements at drum speed of 160 mm/min. The horizontal segment indicates both expiratory pause and jet injection period. The downward segment BC indicates exhalation. Because the spirometer drum rotates from left to right, the tracing is read from right to left.

Jet ventilation performed through a cricothyroid cannula is known to cause several complications including pneumomediastinum.[8] If a tracheal catheter is used, direct laryngoscopy and sometimes a stylet are needed. In addition, the tip of a soft catheter may vibrate when subjected to high pressure jet flows. Moreover, these methods do not always ensure airway visualization. The use of a bronchofiberscope for jet ventilation enables the anesthesiologist to inspect the airway. The bronchoscope tip, which does not vibrate during jet insufflation, can be advanced to a desired location without a stylet. In summary, the built-in suction-biopsy channel of the flexible fiberoptic bronchoscope can be used to deliver prolonged adequate pulmonary jet ventilation.

## REFERENCES

1. Spoerel WE, Narayan PS, Singh NP: Trans-tracheal ventilation. Br J Anaesth 43:932–938, 1971
2. Spoerel WE, Greenway RE: Technique of ventilation during endolaryngeal surgery under general anaesthesia. Can Anaesth Soc J 20:369–377, 1973
3. Cromwell SB, Hirshman CA, McCullough RE, et al: Simplified delivery of volatile anesthetics for bronchoscopy. Anesthesiology 43:377–379, 1975
4. Heifetz M, De Myttenaerê S, Lemer J: Intermittent positive pressure inflation during fiberoptic bronchoscopy. Chest 72: 480–482, 1977
5. Jacobs HB: Emergency percutaneous transtracheal catheter and ventilator. J Trauma 12:50–55, 1972
6. MacNaughton FI: Catheter inflation ventilation in tracheal stenosis. Br J Anaesth 47:1225–1227, 1975
7. Churchill-Davidson HC: A Practice of Anesthesia. Fourth edition. Philadelphia, WB Saunders Co, 1978, p 149
8. Poon YK: A life threatening complication of cricothyroid membrane puncture. Anesth Analg 55:298–301, 1976

ANESTH ANALG
59:355-358, 1980

# Cardiovascular Effects of Anesthetic Induction with Ketamine

**Kenneth Waxman, MD,* William C. Shoemaker, MD,† and Maurice Lippmann, MD‡**

---

WAXMAN, K., SHOEMAKER, W. C., AND LIPPMANN, M.: Cardiovascular effects of anesthetic induction with ketamine. Anesth Analg 59:355–358, 1980.

Anesthetic induction with ketamine has been reported to maintain or improve cardiovascular performance in severely ill patients. Using invasive cardiovascular monitoring, we studied physiologic responses to a single dose of ketamine in 12 critically ill patients. Six patients demonstrated decreases in ventricular contractility, and four had decreases in cardiac output. Mean arterial blood pressure decreased in four patients. Pulmonary venous admixture increased in four of six patients, while oxygen consumption decreased in eight of 11 patients. Thus, a single dose of ketamine produced decreases in cardiac and pulmonary performance and in peripheral oxygen transport in this group of patients. It is proposed that in severely ill patients, preoperative stress may alter the usual physiologic responses to ketamine administration, and adverse effects may predominate. Ketamine, therefore, should be used with caution for induction of anesthesia in critically ill and in acutely traumatized patients until additional studies and further information on cardiovascular responses to ketamine are available.

**Key Words:** ANESTHESIA, Intravenous: ketamine.

---

KETAMINE has been advocated by some as the drug of choice for maintaining or increasing cardiovascular performance during induction of anesthesia, especially in severely ill surgical patients whose cardiovascular status is critical.[1-4] Because of its reported stimulatory cardiovascular effects, ketamine has also been suggested as an agent to administer to casualty victims during major disasters.[5-7]

The studies upon which these recommendations have been based have evaluated the effects of ketamine induction largely in terms of its effects on blood pressure and heart rate. There has been little work documenting the effects of ketamine on cardiac output and oxygen transport, which may be more significant physiologic variables.

The present study summarizes cardiorespiratory responses to induction of anesthesia with ketamine in 12 critically ill surgical patients. The data fail to confirm uniformly beneficial effects of ketamine induction.

## Materials and Methods

### Clinical Material

Patients were chosen for intraoperative monitoring on the basis of the preoperative severity of their illnesses and expected high surgical morbidity and mortality. Of 60 critically ill patients studied over the past year, 12 patients were studied before and after ketamine induction. The patients' clinical and physiologic data are summarized in the Table.

### Physiologic Methods

Triple lumen flow-directed balloon-tipped catheters were placed percutaneously via the internal jug-

---

* Chief Resident in Surgery, Los Angeles County Harbor/UCLA Medical Center.

† Professor of Surgery, UCLA School of Medicine.

‡ Associate Professor of Anesthesia, UCLA School of Medicine.

Received from the Departments of Surgery and Anesthesia, Los Angeles County Harbor/UCLA Medical Center, Torrance, California, and the UCLA School of Medicine, Los Angeles, California. Accepted for publication January 22, 1980.

Reprint requests to Dr. Shoemaker, Department of Surgery, Los Angeles County Harbor/UCLA Medical Center, 1000 West Carson Street, Torrance, California 90509.

**TABLE**
**Clinical and Experimental Data***

| Patient | Diagnosis/operation | Dose | Outcome | Preop BV | Time | HR | MAP | PCWP | CI | LVSW | SVR | $O_2$ ER | $\dot{V}_{O_2}$ | PVR | $\dot{Q}s/\dot{Q}t$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *mg* | | *L/M²* | | *beats/ min* | *mm Hg* | *mm Hg* | *L/M²* | *g·m·M²* | *dyne· cm/ sec⁵·M²* | % | *ml/ min· M²* | *dyne· cm/ sec⁵·M²* | % |
| 1 | Drainage subphrenic abscess | 70 | Survived | 2.80 | B | 120 | 86 | 11 | 5.74 | 56 | 1169 | 21 | 160 | 46 | 33 |
| | | | | | A | 125 | 107 | 19 | 5.00 | 58 | 1557 | 19 | 139 | 80 | 25 |
| 2 | GI bleed-portacaval shunt | 125 | Survived | 2.32 | B | 70 | 84 | 4 | 1.64 | 27 | 3924 | 27 | 67 | 277 | 19 |
| | | | | | A | 96 | 86 | 4 | 2.31 | 28 | 2856 | 17 | 66 | 196 | 43 |
| 3 | GI bleed-portacaval shunt | 110 | Survived | 3.64 | B | 80 | 91 | 6 | 4.99 | 80 | 1421 | 19 | 153 | 96 | 37 |
| | | | | | A | 78 | 58 | 6 | 3.45 | 35 | 1274 | 24 | 129 | 77 | 31 |
| 4 | GI bleed-portacaval shunt | 110 | Survived | 3.60 | B | 87 | 97 | 8 | 5.01 | 76 | 1472 | 13 | 89 | 128 | 48 |
| | | | | | A | 105 | 71 | 15 | 5.23 | 49 | 1004 | 10 | 69 | 97 | 58 |
| 5 | Sepsis-intra-abdominal abscess-drainage | 60 | Died | 2.61 | B | 110 | 83 | 9 | 3.58 | 38 | 1673 | 33 | 166 | 261 | — |
| | | | | | A | 108 | 55 | 6 | 3.55 | 26 | 1075 | 16 | 74 | 328 | — |
| 6 | Sepsis-intra-abdominal abscess-drainage | 50 | Died | — | B | 155 | 66 | 20 | 4.86 | 28 | 821 | 46 | 274 | 159 | 16 |
| | | | | | A | 165 | 75 | 17 | 5.25 | 33 | 909 | 18 | 121 | 218 | 50 |
| 7 | CRF, bleed-diverticulitis colectomy | 70 | Survived | 2.90 | B | 68 | 111 | 17 | 4.60 | 102 | 1751 | 24 | 139 | 168 | — |
| | | | | | A | 67 | 101 | 15 | 4.38 | 90 | 1666 | 19 | 117 | 213 | — |
| 8 | Sepsis-intraabdominal abscess-drainage | 90 | Died | — | B | 84 | 102 | 6 | 3.12 | 52 | 2615 | 30 | 120 | 281 | — |
| | | | | | A | 90 | 133 | 22 | 3.04 | 61 | 3365 | 23 | 105 | 417 | — |
| 9 | UGI bleed-gastrectomy | 140 | Survived | 2.64 | B | 120 | 117 | 17 | 3.81 | 51 | 2254 | — | — | — | — |
| | | | | | A | 120 | 124 | 10 | 3.64 | 51 | 2509 | — | — | — | — |
| 10 | Perforated duodenal ulcer-vagotomy and pyloroplasty | 75 | Died | 2.20 | B | 110 | 93 | — | 2.93 | 34 | 2290 | 39 | 156 | — | — |
| | | | | | A | 60 | 40 | — | 2.24 | 21 | 1390 | 61 | 169 | — | — |
| 11 | Sepsis-perforated cholecystitis-cholecystectomy | 25 | Died | — | B | 96 | 101 | 20 | 3.14 | 45 | 1983 | 26 | 120 | 224 | — |
| | | | | | A | 90 | 97 | 21 | 2.91 | 43 | 2059 | 27 | 102 | 160 | — |
| 12 | GI bleed-portacaval shunt | 115 | Survived | 3.61 | B | 76 | 87 | — | 3.26 | 51 | 1960 | 20 | 92 | 82 | 6 |
| | | | | | A | 76 | 87 | — | 3.21 | 50 | 1980 | 17 | 81 | 125 | 36 |

* Abbreviations used are: Preop BV, preoperative blood volume; HR, heart rate; MAP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; LVSW, left ventricular stroke work; SVR, systemic vascular resistance; $O_2$ ER, oxygen extraction; $\dot{V}_{O_2}$, oxygen consumption; PVR, pulmonary vascular resistance; $\dot{Q}s/\dot{Q}t$, pulmonary venous admixture; B, before ketamine; A, after ketamine; GI, gastrointestinal; CRF, chronic renal failure; UGI, upper gastrointestinal.

ular vein, and arterial lines via the radial arteries in the intensive care unit prior to preoperative medication. Blood volumes were measured preoperatively with $^{125}$I-labeled albumin (RISA) using previously described techniques.[8] Cardiac output was measured by thermodilution using a cardiac output computer (Edwards Laboratory, model 9520, Santa Ana, CA). Systemic and pulmonary arterial pressures, heart rate (HR), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP), hemoglobin, hematocrit, and arterial and mixed venous blood gas tensions were measured. Left ventricular stroke work (LVSW), systemic vascular resistance (SVR), and pulmonary vascular resistance, pulmonary venous admixture ($\dot{Q}s/\dot{Q}t$), oxygen extraction ($O_2$ER), and oxygen consumption ($\dot{V}_{O_2}$) were calculated using standard formulas.[9] All pressure and volume measurements were indexed to body surface area.

## Protocol

Upon arrival in the operating room, 100% $O_2$ was administered by mask and continued throughout the period of observation. After monitoring equipment was connected and calibrated, control measurements were made in duplicate. Ketamine was then given intravenously over 1 minute in doses varying from 24 to 144 mg; the mean dose was 70 mg. Measurements were then repeated 3 to 5 minutes after ketamine administration, again in duplicate. No other medications were given to these patients, nor was controlled ventilation or endotracheal intubation instituted during the period of study. On two occasions in the present series and in several instances in other ketamine studies, measurements were repeated 10 minutes or more after ketamine administration in an attempt to evaluate the time course of the ketamine response. In general, the responses at 10 or more minutes after ketamine were in the same direction but less pronounced. However, it was not considered appropriate to obtain the entire time course as many other interventions, such as tracheal intubation, changes in $F_{IO_2}$, and mechanical ventilation, were urgently needed at this time. The present study, therefore, is confined to the evaluation of ketamine effects at 5 minutes.

## Results

The results are summarized in the Table.

### Heart Rate (HR)

Eleven patients maintained or increased their HR. One patient, however, developed a significant bradycardia, with reduced arterial pressure and cardiac output.

### Mean Arterial Pressure (MAP)

Seven patients maintained or increased their MAP. However, in four patients, MAP decreased more than 15% from control values. In three of those patients, MAP decreased to below 60 mm Hg.

### Cardiac Index (CI)

While most patients maintained CI at or near control values, four of the twelve patients had reductions of cardiac index greater than 10%.

### Myocardial Performance

Six patients had either decreases in left ventricular stroke work or increases in pulmonary capillary wedge pressure after ketamine, signifying decreased cardiac contractility; mean systemic resistance was not consistently increased during this period. In one patient, stroke work increased and wedge pressure decreased, suggesting improved myocardial function; since systemic resistance decreased after ketamine administration in this patient, the apparent improvement in performance may have been due to decreased afterload.

### Systemic Vascular Resistance (SVR)

SVR decreased in six and increased in six patients. Pulmonary vascular resistance increased in six of 10 patients in whom measurements were available.

### Pulmonary Venous Admixture or Shunt ($\dot{Q}s/\dot{Q}t$)

$\dot{Q}s/\dot{Q}t$ increased significantly after ketamine in four of six patients in whom it was measured.

### Oxygen Consumption ($\dot{V}_{O_2}$)

$\dot{V}_{O_2}$ decreased in eight of 11 patients. This decrease, associated with reduced oxygen extraction, did not correlate well with decreases in CI.

## Discussion

Induction of anesthesia in critically ill patients often has adverse physiologic effects. Nearly every anesthetic agent studied has potential for cardiovascular depression; this depression may be poorly tolerated by the severely ill patient who is compensating maximally preoperatively and has little physiologic reserve. The development of anesthetic agents that may be cardiovascular stimulants clearly represents a major advance. It is important to evaluate such agents clinically in the critically ill patient in whom the induction period is most hazardous.

In this series of critically ill patients, ketamine clearly was not without adverse effects. Ketamine has been reported to be a positive inotropic agent.[1, 2] but in this series, half of the patients had decreased cardiac contractility following induction with ketamine. Further, cardiac output increased in only one patient, and this was associated with decreased afterload.

Pulmonary function also may be adversely affected by ketamine induction of anesthesia, as demonstrated by an increase $\dot{Q}s/\dot{Q}t$ in four of six patients. The cause for this impairment is not readily apparent from these data, but it is possible that ketamine produced maldistribution of blood flow within the pulmonary vasculature.[10, 11]

Finally, in a majority of these patients, oxygen extraction and $\dot{V}_{O_2}$ decreased after ketamine administration. This is at variance with the results of Gooding et al,[12] who showed little change in $\dot{V}_{O_2}$ after ketamine induction in patients undergoing elective skin grafting. Whether the decrease in $\dot{V}_{O_2}$ we observed in these critically ill patients was due to decreased metabolic demands associated with ketamine, or whether it represented maldistribution of systemic blood flow resulting in inadequate tissue oxygenation is an unanswered question.

Stimulatory cardiovascular effects of ketamine are currently thought to involve several mechanisms. Ketamine may directly stimulate the central sympathetic nervous system releasing catecholamines.[13, 14] Further, ketamine may inhibit neuronal and extraneuronal reuptake of norepinephrine, thereby increasing tissue and circulating norepinephrine levels.[15] In addition, Oyama and associates[16] have noted elevated serum cortisol levels during ketamine anesthesia, and propose adrenocortical stimulation. However, none of this work is based on studies of seriously ill patients. The patients we have studied were septic, hypovolemic, or cirrhotic, and had severe stress preoperatively. It is possible that in these ill patients adrenocortical and catechol stores had been depleted prior to ketamine administration. Alternatively, in the setting of prolonged preoperative stress, there may be resistance to further sympathetic and/or adrenocotical stimulation by ketamine. In either case, preoperative stress may blunt the usual physiologic responses to ketamine, setting the stage for possible adverse effects.

In order to simplify interpretation, we have examined only the effects of a single dose of ketamine, soon after its administration. It is possible these effects may change with time, and in response to administration of other anesthetic agents, paralysis, and intubation. Still more important a question is how these patients would have responded to alternative modes of induction; i.e., was ketamine better than anything else despite its adverse effects? We have certainly seen even more profound adverse effects with other induction agents (K. Waxman, W. C. Shoemaker, and M. Lippmann, unpublished data). It will require a randomized prospective comparison of ketamine and other agents to answer these questions. We conclude, however, that in the critically ill patient, induction of anesthesia with ketamine may be associated with decreases in cardiac and pulmonary function, as well as with decreases in $\dot{V}_{O_2}$.

## REFERENCES

1. Tweed WA, Minuck M, Mymin D: Circulatory response to ketamine anesthesia. Anesthesiology 37:613–619, 1972
2. Nettles DC, Herrin TJ, Mullen JG: Ketamine induction in poor-risk patients. Anesth Analg 52:59–64, 1973
3. Langrehr D, Neuhaus R, Singbartl G: Ketamine: special indications and controversial aspects, in Recent Progress in Anaesthesiology and Resuscitation: Proceedings of the IV European Congress. Edited by A Arias et al. New York, Elsevier, 1975, pp 81–86
4. Gallagher TJ: Assessment and anesthesia for multiple trauma patients, in Proceedings of the First International Congress on Disaster Medicine. Edited by R Frey and P Safar. New York, Springer-Verlag, in press 1980
5. Rust M, Landauer B, Kolb E: The value of ketamine in emergency situations. Anaesthesist 27:205–212, 1978
6. Corssen G: The use of ketamine hydrochloride for relief of pain and suffering in disaster situations, in Proceedings of the First International Congress on Disaster Medicine. Edited by R Frey and P Safar. New York, Springer-Verlag, in press 1980
7. Kamm G: General and local anaesthesia in disaster situation, in Proceedings of the First International Congress on Disaster Medicine. Edited by R Frey and P Safar. New York, Springer-Verlag, in press 1980
8. Shoemaker WC: Effects of transfusion on surviving and nonsurviving postoperative patients. Surg Gynecol Obstet 142:33–40, 1976
9. Shoemaker WC, Montgomery ES, Kaplan E, et al: Physiologic patterns in surviving and nonsurviving shock patients. Arch Surg 106:630–636, 1973
10. Tiefenbrun J, Shoemaker WC: Sequential changes in pulmonary blood flow distribution in hemorrhagic shock. Ann Surg 174:727–733, 1972
11. Brown RS, Kim SI, Shoemaker WC: Hemodynamic mechanisms in the development of pulmonary venous admixture (shunting). J Surg Res 17:192–199, 1974
12. Gooding JM, Dimick AR, Tavakoli M, et al: A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. Anesth Analg 57:813–816, 1977
13. Slogoff S, Allen GW: The role of baroreceptors in the cardiovascular response to ketamine. Anesth Analg 53:704–707, 1974
14. Chang P, Chan KE, Ganendran A: Cardiovascular effects of 2-(O-chlorophenyl)-2-methylaminocyclohexanone (CI-581) in rats. Br J Anaesth 41:391–395, 1969
15. Salt PJ, Barnes PK, Beswick FJ: Inhibition of neuronal and extraneuronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. Br J Anaesth 51:835–838, 1979
16. Oyama T, Matsumoto F, Kudo T: Effects of ketamine on adrenocortical function in man. Anesth Analg 49:697–700, 1970

ANESTH ANALG
59:359-366, 1980

# Assessment of Vaporizer Performance in Low-Flow and Closed-Circuit Anesthesia

Chung-Yuan Lin, MD*

---

LIN, C.-Y.: Assessment of vaporizer performance in low-flow and closed-circuit anesthesia. Anesth Analg 59:359-366, 1980.

The performance of five of the most commonly used halothane vaporizers and three enflurane vaporizers was tested under conditions encountered in low-flow and closed-circuit anesthesia. Anesthetic gas concentrations were measured continuously with a mass spectrometer connected to a circle system. The results indicated that all of the units tested, except the Fluotec Mark II, may be adapted for use in low-flow or closed-circuit anesthesia to provide accurate amounts of potent inhalation anesthetics. One should be aware, however, that the concentration of nitrous oxide affects vaporizer output, that changes in output occur during positive-pressure ventilation, and that the output of some of the vaporizers may increase when a change from high flow to low flow is made. It is also strongly recommended that upstream oxygen flushing be abandoned in the practice of low-flow or closed-circuit anesthesia.

**Key Words:** EQUIPMENT: vaporizers; ANESTHETIC TECHNIQUES: closed circuit.

---

IN VIEW of the renewed interest in closed-circuit or low-flow anesthesia, we critically evaluated the performance of several vaporizers, paying special attention to low gas flows. The flows that we used may be considered as going beyond the recommendations of the vaporizer manufacturers; nevertheless, we used these vaporizers with low flows because they are often attached to anesthesia machines that may be and frequently are used in low-flow and closed anesthesia circuits. We sought to determine whether these existing vaporizer models can be safely used at the low gas flows required for closed-circuit anesthesia.

## Methods

The most commonly used vaporizers for halothane (Fluotec Mark II, III, Fluomatic (Foregger), Ohio, and Dräger Vapor) and for enflurane (Cyprane, Ohio, Dräger Vapor, and Dräger Vapor 19) were evaluated in an anesthetic circuit which simulated various clinical situations. An Ohio Medical Company oxygen flow meter delivered oxygen into the circuit. An anesthetic machine (Ohio Unitrol) with an outlet for oxygen and nitrous oxide was connected to the test vaporizer, and the vaporizer outlet was connected to the fresh-gas inlet of a circle system. The patient connection was replaced with a rubber bag of 3000-ml capacity. The circuit was ventilated with an Air Shields ventilator at various volumes. A pressure monitor and a mass spectrometer sampling connector were placed between the vaporizer outlet and the fresh-gas inlet of the circle system. Pressure changes at the vaporizer outlet were measured continuously with a Trantec transducer and recorded on a Gould 220 dual-channel recorder. The concentration of halothane or enflurane vapor was monitored continuously with the mass spectrometer and recorded on paper.

The mass spectrometer used in this study was a Perkin-Elmer model 1100. This unit was calibrated with gas supplied for this purpose by Union Carbide

---

* Associate Professor.

Supported in part by Oppenheimer Endowment #1 6-3360-38-6609.

Received from the Department of Anesthesiology, The University of Chicago, 950 East 59th Street, Chicago, Illinois 60637. Accepted for publication January 22, 1980.

Company. The accuracy of the readings was further confirmed in our laboratory by gas chromatography. We used the mass spectrometer, with a 90% response time of less than 500 msec, to ascertain accurately "on line" the continuous output capability of the vaporizers. For halothane, two Fluotec Mark II, two Fluotec Mark III, one Fluomatic, five Ohio, and four Dräger Vapor vaporizers, and for enflurane, two Cyprane, five Ohio, three Dräger Vapor, and two Dräger Vapor 19 vaporizers were tested in this way. Except for the Fluotec Mark II, all vaporizers tested were new units. We evaluated the vaporizers in a room maintained at a temperature of 25 C.

## Results

We carried out the following six tests with the following results.

### 1. Matching Direct Measurement of Vapor Concentration against Dial Setting of Vaporizer Output at Various Flows

As shown in Fig 1 and Table 1, all of the units tested except the Fluotec Mark II performed quite adequately. Output agreed closely with the manufacturer's data with free flows into ambient air at rates ranging from 100 to 5000 ml/min.

### 2. Determination of Accuracy of Vaporizer Output When Flow was Changed Abruptly

Abrupt changes in gas flow from high to low values are frequent during low-flow or closed-circuit anesthesia. Three vaporizers, Fluotec Mark III, Fluomatic, and Dräger Vapor, showed minimal changes in output concentrations when flows through the vaporizer were changed abruptly from 5000 to 1000 ml/min to 500 ml/min (Fig 2). In contrast, the Ohio unit exhibited considerable changes in output, as shown in Fig 2, when the flow was changed suddenly from higher to lower values.

### 3. Determination of Possible "Pumping Effect"

Numerous investigators have shown that a factor of great significance with out-of-circuit vaporizers, such as the five types that we tested, is the effect of fluctuations in the vaporizer output due to the back-pressure generated during assisted or controlled ventilation. This back-pressure causes increased vapor concentration, referred to as a pumping effect, or decreased concentration, referred to as "pressurizing effect." The pumping effect observed with the Ohio unit is shown in Fig 3. There was marked fluctuation in the vaporizer output concentration when we applied back-pressure by attaching the vaporizer output to the circle system and employed controlled respiration. The Fluotec Mark II showed significant and erratic increases in output concentration when positive pressure was applied at flows of 2000 ml/min (Fig 4) or lower dial settings. This result and the lower output concentration shown in Fig 1 with Fluotec Mark II at a lower dial setting and lower flow indicate that a relatively higher resistance to flow exists in this vaporizing chamber. At a gas flow of 5000 ml/min, fluctuation in output concentration was seen (Fig 4, upper panel), but the mean vapor output did not change with the Ohio and Fluotec Mark II units tested. The back-pressure effect was not seen in the three other vaporizers studied.

### 4. Determination of Possible "Pressurizing Effect"

Cole[1] found that the concentration of anesthetics delivered by vaporizers was lower during positive-pressure respiration (pressurizing effect) than during free flow to the atmosphere. We found no demonstrable pressurizing effect with Fluotec Mark III, Dräger, or Fluomatic vaporizers with continuous positive pressure up to 15 cm $H_2O$. The Ohio vaporizer consistently had an initial decrease in output, but returned to the predicted levels within seconds. With both the Ohio and Fluotec Mark II vaporizers, a marked but transient elevation in output concentration occurred upon abrupt cessation of positive pressure.

### 5. Determination of Possible Effects Resulting from Upstream Oxygen Flushing

The Fluotec Mark III demonstrated only a negligible effect on vaporizer output due to upstream oxygen flushing. With Ohio, Dräger, and Fluomatic vaporizers, oxygen flushing increased halothane concentrations more than 10% during several seconds at low initial fresh-gas flows.

### 6. Determination of Possible Effects Due to Addition of Nitrous Oxide as Carrier Gas

As shown in Fig 5, all units tested except the Fluotec Mark II showed stepwise decreases in halothane vapor output with stepwise increases in nitrous oxide concentration at a time when total gas flow remained constant. When the carrier gas was changed from 100% oxygen to 100% nitrous oxide, the halothane

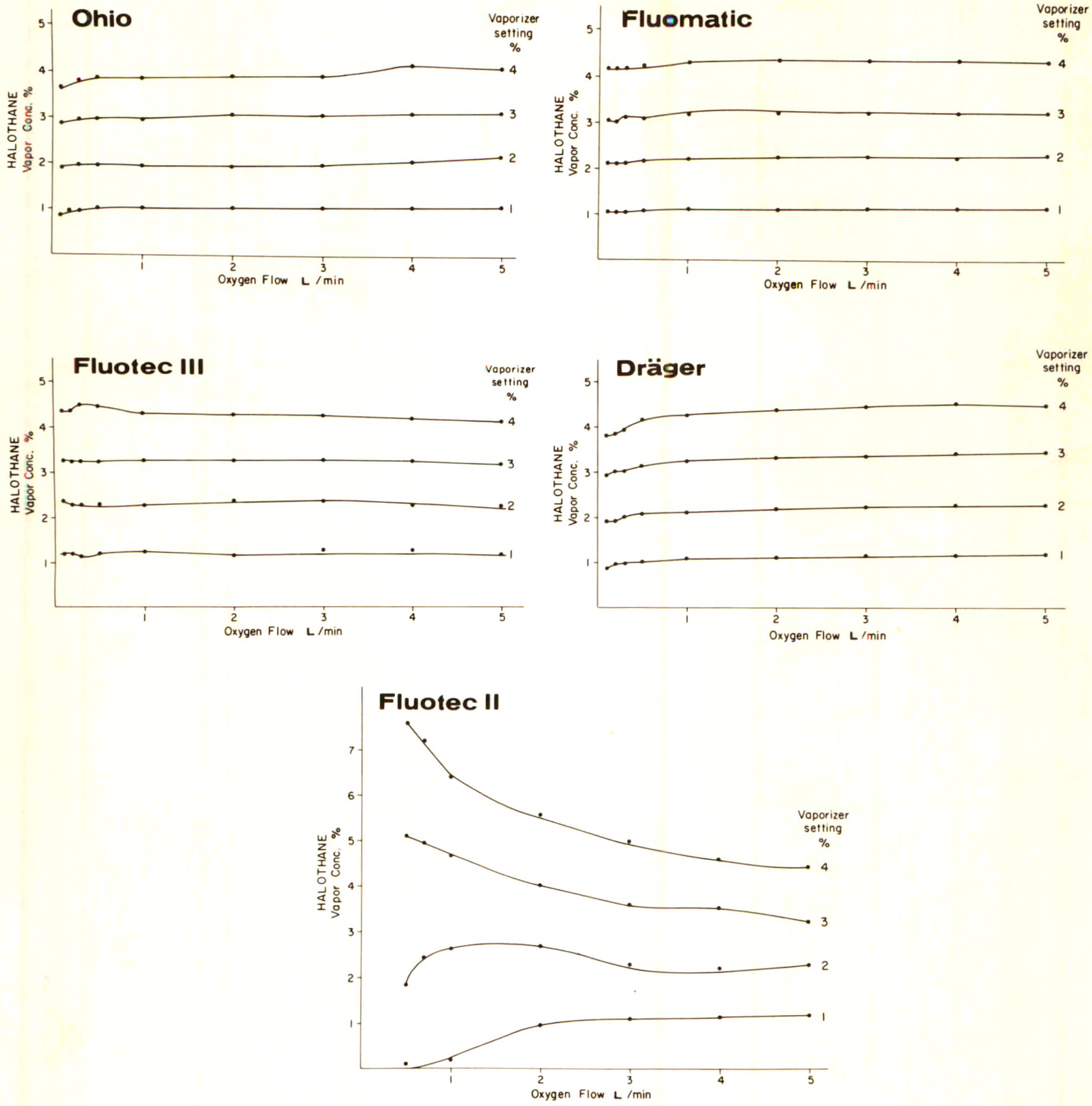


FIG 1. Calibration of vaporizer outputs during free flow into ambient air at various settings from 1% to 4% halothane and with flows ranging from 100 to 5000 ml/min. All experiments performed at 25 C.

**TABLE 1**

**Actual Output of Halothane of Five Vaporizers Tested**

| Vaporizer output concentration (%) at 1% dial setting | Ohio (n = 5) | Fluomatic (n = 1) | Dräger Vapor (n = 4) | Fluotec Mark II (n = 2) | Fluotec Mark III (n = 2) |
|---|---|---|---|---|---|
| Total gas flow at | | | | | |
| 5000 ml/min | 1.07 ± 0.06 | 1.12 | 1.10 ± 0.08 | 1.10 ± 0.03 | 1.08 ± 0.06 |
| 500 ml/min | 1.00 ± 0.09 | 1.08 | 1.03 ± 0.07 | 0.08 ± 0.11 | 1.12 ± 0.06 |

vapor output decreased by 20 to 35%. This change was consistent at both high and low total gas flows through the Fluomatic, Fluotec Mark III, and Dräger vaporizers, but not the Ohio vaporizer. The Fluotec Mark II unit showed a slight increase in halothane vapor output when nitrous oxide was included in the carrier gas. The increase was, however, only transient;

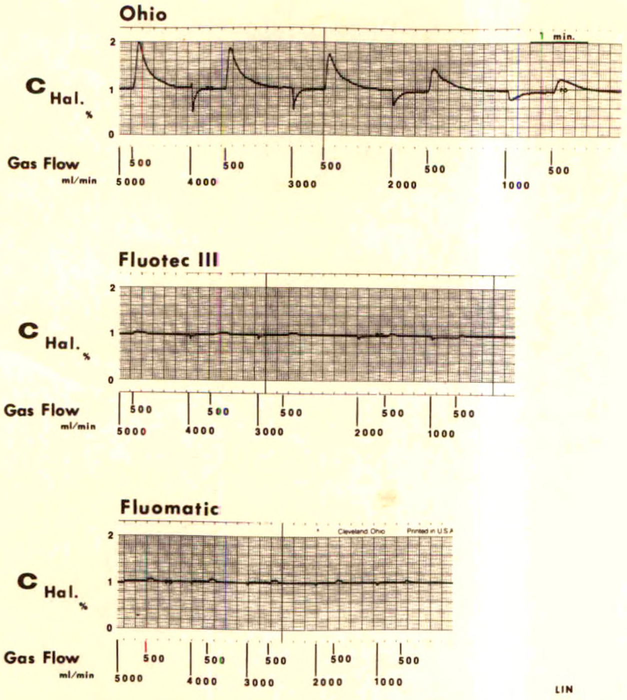


FIG 2. Effect on halothane output of vaporizer when high flow is suddenly reduced. The Ohio vaporizer was associated with a transient, but significant increase in vapor output, the magnitude of which was related to the magnitude of the initial high flow. A transient reduction in vapor output occurred when the flow was increased from low to high. There were no significant changes with Fluotec Mark III and Fluomatic vaporizers.

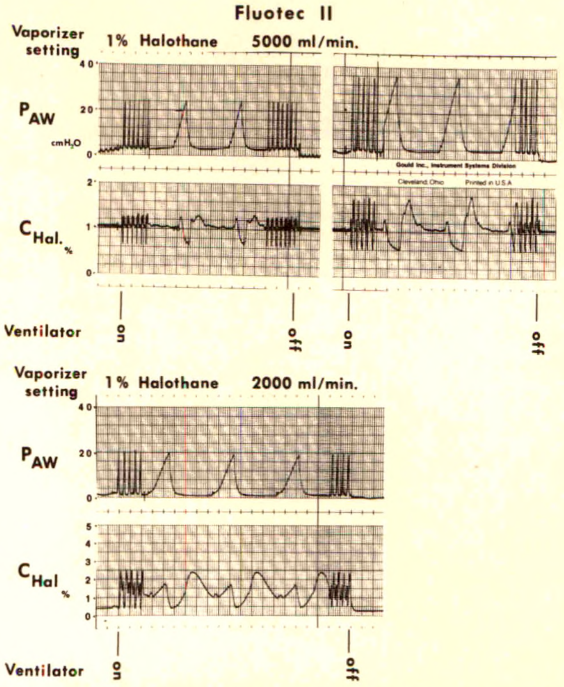


FIG 4. Effect of positive-pressure ventilation ($P_{AW}$, upper tracings) on vapor output (lower tracings) of the Fluotec Mark II vaporizer. A significant fluctuation in vapor output is demonstrated; the amplitude of the fluctuation is related to changes in pressure during positive-pressure ventilation. The lower panel shows that the changes were more pronounced at oxygen flows of 2000 ml than they were with $O_2$ flows of 5000 ml/min. At 2000 ml/min, the mean vapor output was more than twice the expected amount, but at 5000 ml/min, the mean vapor output remained unaltered.

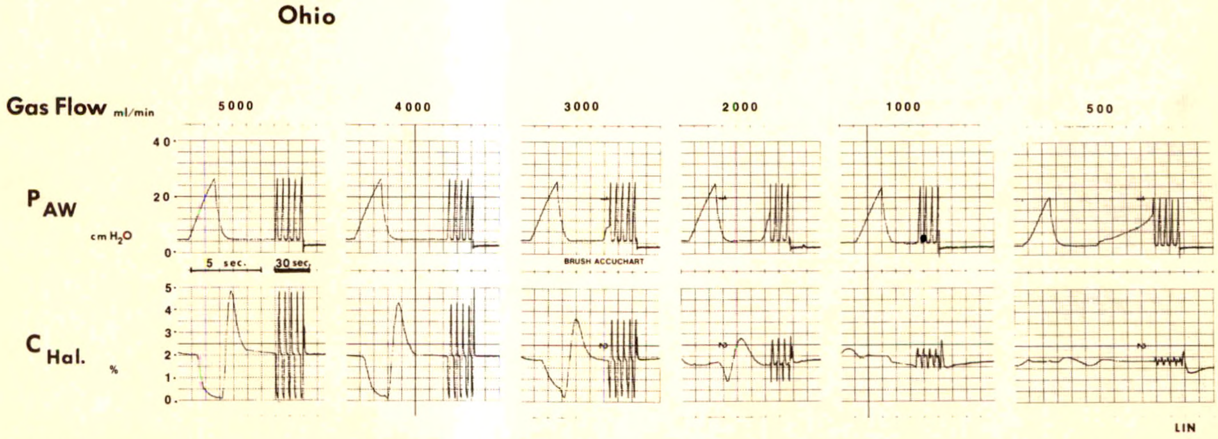


FIG 3. Effect of positive-pressure ventilation (upper tracings) on the vapor output of the Ohio vaporizer. Output vapor concentration (lower tracings) significantly changed as a function of gas inflow and pressure: the higher the gas flow, the greater the fluctuation. At the highest flow tested, 5000 ml/min, output reached 5% immediately after positive pressure was released even though the dial setting remained at 2%. In spite of these fluctuations, mean mass vapor output did not change from the setting for free flow to the atmosphere. Each record shows time scale in the left tracing expanded to 10 times that on the right. $P_{AW}$, Airway pressure.

the duration of the change depended upon the dial setting and the total gas flow through the vaporizer. As shown in Fig 6, at total gas flows of 5000 or 3000 ml/min, the change only lasted for 5 to 10 minutes with an Ohio vaporizer, but at a total gas flow of 500 ml/min, recovery had not occurred after 50 minutes. We also observed that when a switch was made from nitrous oxide or a nitrous oxide-oxygen mixture to 100% oxygen while the vaporizer was turned on, the vaporizer output increased by 20 to 280% for 5 to 60 minutes depending on the total gas flow and the previous nitrous oxide concentration. Tables 2 and 3 summarize the effect of 100% nitrous oxide or 50% nitrous oxide on a vaporizer dial setting with 3000 ml/min total gas flow. For most of the units tested, the standard deviation was less than 10% of the actual vapor concentration output.

### 7. Enflurane Vaporizers

The characteristics and extent of the changes in vaporizer output due to the pumping effect, pressurizing effect, and change in carrier gas (Fig 7) were similar to changes that occurred with halothane vaporizers.

## Discussion

Many studies[2] have confirmed the presence of anesthetic gas pollution in operating rooms. The principal measures for combating this potential health hazard include removal of anesthetic waste by scavenger devices[3] and use of low-flow and closed-circuit techniques. Low-flow or closed-circuit anesthesia requires delivery of accurately measured amounts of vaporized gases into the anesthetic circuit.

When positive-pressure ventilation is used, backpressure may be exerted on the vaporizer and may cause either increases or decreases in output of anesthetic vapor; this phenomenon has been termed a pumping effect[4] or pressurizing effect.[1] Attempts have been made to correct this deficiency by incorporation of a relief valve at the outlet port of the vaporizer to limit the maximal pressure, by reduction in the size of the vaporizing chamber, and by addition of a long spiral tube leading to the vaporizing chamber.[5–7]

**TABLE 2**

**Nitrous Oxide Effect with 1% Dial Setting of Halothane (3000 ml/min Total Gas Flow)**

| Carrier gas change | Ohio (n = 5) | | Fluomatic (n = 1) | | Dräger (n = 4) | | Fluotec Mark III (n = 2) | |
|---|---|---|---|---|---|---|---|---|
| | Change | Duration | Change | Duration | Change | Duration | Change | Duration |
| | % | min | % | min | % | min | % | min |
| 100% $O_2$ → 100% $N_2O$ | −44.8<br>±2.2 | 9.9<br>±0.9 | −20.0 | 8.0 | −18.4<br>±0.5 | 9.1<br>±0.3 | −15.8<br>±0.4 | 9.3<br>±0.4 |
| 100% $O_2$ → 50% $N_2O$ | −20.0<br>±1.5 | 9.7<br>±0.6 | −11.0 | 7.0 | −9.3<br>±0.7 | 8.9<br>±0.3 | −7.3<br>±0.4 | 9.0<br>±0.0 |
| 100% $N_2O$ → 100% $O_2$ | 182.0<br>±66.0 | 16.6<br>±1.9 | 22.0 | 8.5 | 19.4<br>±0.5 | 9.4<br>±0.5 | 21.5<br>±0.7 | 9.5<br>±0.7 |
| 50% $N_2O$ → 100% $O_2$ | 27.6<br>±2.1 | 14.5<br>±1.3 | 12.0 | 8.0 | 9.6<br>±0.5 | 9.3<br>±0.5 | 12.5<br>±0.7 | 9.5<br>±0.7 |

**TABLE 3**

**Nitrous Oxide Effect with 1% Dial Setting of Enflurane (3000 ml/min Total Gas Flow)**

| Carrier gas change | Ohio (n = 5) | | Cyprane (n = 2) | | Dräger Vapor (n = 3) | | Dräger Vapor 19 (n = 2) | |
|---|---|---|---|---|---|---|---|---|
| | Change | Duration | Change | Duration | Change | Duration | Change | Duration |
| | % | min | % | min | % | min | % | min |
| 100% $O_2$ → 100% $N_2O$ | −55.4<br>±2.4 | 14.4<br>±1.1 | −18.5<br>±2.1 | 6.1<br>±0.5 | −18.8<br>±0.8 | 8.8<br>±0.8 | −20.8<br>±0.4 | 9.5<br>±0.7 |
| 100% $O_2$ → 50% $N_2O$ | −25.4<br>±1.8 | 13.0<br>±1.2 | −8.2<br>±0.5 | 5.4<br>±0.3 | −9.1<br>±0.4 | 8.5<br>±0.5 | −10.5<br>±0.7 | 8.8<br>±0.4 |
| 100% $N_2O$ → 100% $O_2$ | 142.0<br>±32.5 | 14.0<br>±1.6 | 19.5<br>±2.1 | 9.9<br>±0.5 | 19.7<br>±1.5 | 9.8<br>±1.3 | 20.3<br>±0.4 | 10.5<br>±0.7 |
| 50% $N_2O$ → 100% $O_2$ | 29.2<br>±1.8 | 13.6<br>±1.1 | 10.3<br>±1.1 | 9.3<br>±0.3 | 10.3<br>±1.5 | 10.2<br>±1.0 | 10.3<br>±0.4 | 9.7<br>±0.2 |

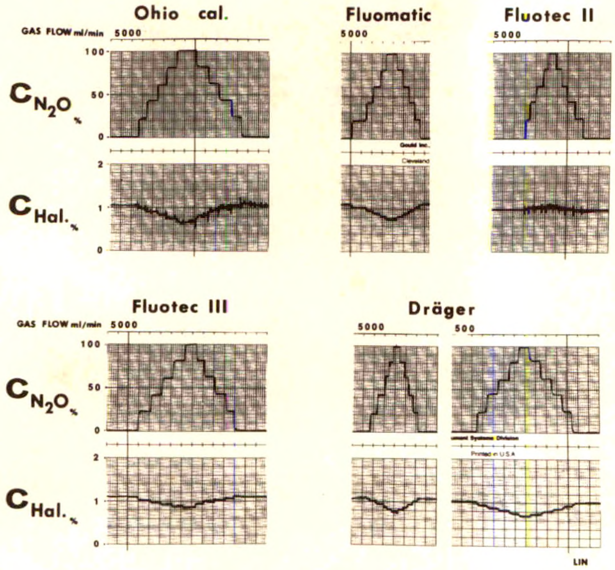


FIG 5. Vaporizer output of Ohio, Fluomatic, Fluotec Mark III, and Dräger vaporizers decreased as nitrous oxide concentration (in oxygen) increased at a time when total gas flow remained constant. Maximum reduction in halothane output was 34%. Reductions occurred at both high and low flows. A slight elevation of vapor output was seen with the Fluotec Mark II as the nitrous oxide concentration increased.

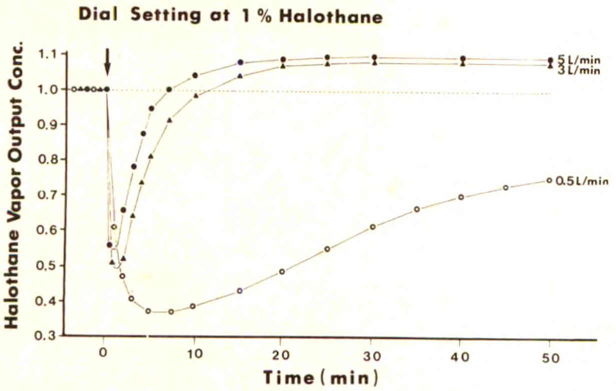


FIG 6. Transient decrease of 50% and more in halothane vapor output from an Ohio vaporizer occurred when the carrier gas was switched from 100% $O_2$ to 100% $N_2O$ at time zero for 5 minutes. The magnitude and duration of the decrease depended on the flow rate of the carrier gas.

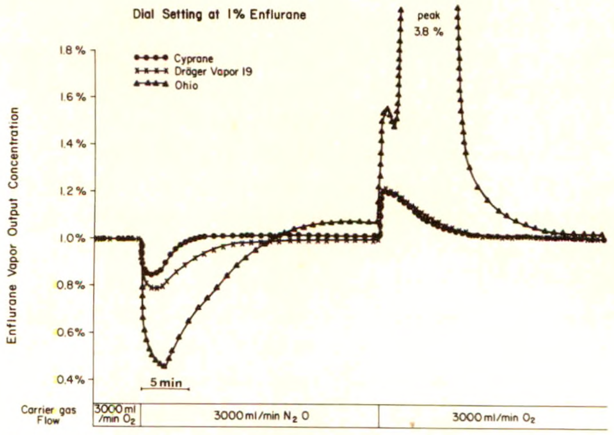


FIG 7. Effect of changes in carrier gas on outputs of the three enflurane vaporizers at a flow rate of 3000 ml/min. The changes were most prominent in the Ohio vaporizer in both duration and magnitude. They were less pronounced in the Cyprane and Dräger Vapor 19 vaporizers.

With the exception of the Fluotec Mark II, all vaporizers tested performed reasonably well, especially in matching the directly measured halothane concentration with that given by the dial setting. These good results were obtained both with free flow to the atmosphere and with a continuous positive back-pressure of up to 15 cm $H_2O$.

The performance of the Fluotec Mark II vaporizer has been studied extensively in the past.[8–11] As shown in our results, below flow rates of 2000 ml/min and at dial settings of less than 2%, this vaporizer delivers a concentration of vapor less than that indicated by the dial. At dial settings above 2% and with flow rates of less than 2000 ml/min, the output is higher than shown by the dial setting. This widely variable output at low fresh-gas flows was further modified by back-pressure. It is apparent that the large vaporizing chamber, small bypass, and short distance to the vaporizing chamber cause a lack of reliability in vapor output at low-flow settings with this vaporizer. Therefore, the Fluotec Mark II unit is not suitable for low-flow or closed-circuit anesthesia.

All five of the Ohio units that we investigated displayed wide fluctuations in vaporizer output in the presence of back-pressure in spite of the check valve which was incorporated in the outlet port. This effect was especially striking at high gas flows and with large-volume ventilation, which revealed that the check valve was inefficient. We removed this valve and found that there was no significant difference in the vaporizer output with or without the valve. Evidently, the valve could not overcome the pressure created by high forward flows of gas and thus remained open throughout. Although marked fluctuations in vapor concentration were present, the mean mass output of vapor actually delivered did not differ from the output measured during free flow to the atmosphere unimpeded by positive-pressure phases.

The most striking finding in this study was the modifying effect of nitrous oxide on the vaporizer output. In 1971, Stoelting[8] demonstrated that the delivered halothane concentration increased slightly at dial settings below 1% when 60% nitrous oxide was a part of the carrier gas, as compared to the concentration with oxygen alone. Diaz[12] further reported that the output of the Fluotec Mark II at the 0.5% and 1% settings was higher with nitrous oxide as the carrier gas; at 2.3% and 4% settings, however, it was higher with oxygen. Diaz also found the Dräger Vapor and Fluomatic halothane vaporizer outputs at all dial settings to be higher with oxygen as the carrier gas than with helium or nitrous oxide. Our findings confirm the trend observed by Diaz[12] and Stoelting,[8] but, as shown in the results, the change is transient. When the previous carrier gas is being washed out of the vaporizer chamber by the new carrier gas, the flow distribution between the bypass and the chamber must return to normal for the vapor output to return to its original level. The direction of the change in halothane output is determined by the relative viscosities of oxygen and nitrous oxide (203.31 and 145.6, respectively), as indicated by Diaz.

The magnitude and duration of the reduction in halothane concentration when the carrier gas was changed from oxygen to nitrous oxide were different for different vaporizers. The Ohio vaporizer exhibited the most prominent reduction, which is most probably related to its construction and the size of the vaporizer chamber. These observed reductions in halothane concentration were related to the vaporizer dial setting, the concentration of nitrous oxide, and the total gas flow through the vaporizer. The higher the flow, the less the reduction and its duration; the lower the dial setting, the greater the reduction and its duration; and the greater the concentration of nitrous oxide, the greater the reduction. In the Ohio vaporizer, contrary to the decrease in halothane vapor output when carrier gas is changed from $O_2$ to $N_2O$ or to a mixture of $N_2O$ and $O_2$, when the reverse change is made the clinical impact may be greater, since the vaporizer output was found to increase by 20 to 380% for periods of 5 minutes or longer depending on the dial setting and total gas flow used. Much less augmentation in vapor output was demonstrated when carrier gas with any percentage mixture of $N_2O$ and $O_2$ was changed to $O_2$ than when 100% $N_2O$ was changed to 100% $O_2$ (see Tables 2 and 3).

In clinical practice, $N_2O$ is rarely turned off before the vaporizer is turned off, but one must keep in mind that these changes may produce significant clinical effects.

In contrast to previous reports,[13, 14] for enflurane vaporizers,[15] the results were similar to those obtained for halothane vaporizers (see Tables 2 and 3).

Several vaporizers, specifically the Ohio and Dräger, exhibited significant although transient elevations in concentration of vapor output up to 2% above the control value when changed from high flows to a low flow of approximately 500 ml/min. Such a maneuver may well be used clinically during low-flow and closed-circuit anesthesia. The additional vapor output generated by the mechanisms outlined above is not very large, amounting to no more than 5 ml of 100% vapor. However, one should be aware of this when using closed-circuit anesthesia and low fresh-gas flows.

Especially at low-flow settings, the quantitative effect of upstream oxygen flushing is impressive. Thus, the peak concentration can exceed 10% with the Fluomatic vaporizer, an effect which persists for more than 10 seconds (Fig 7).

During recent years, the mass spectrometer has become portable, accurate and versatile enough for many clinical applications; it is no longer an instrument for research only. In routine clinical practice, the mass spectrometer can be utilized for continuous monitoring not only of concentrations of anesthetics but also of concentrations of $CO_2$, $O_2$, and $N_2$. As the results reported here show, the mass spectrometer can also be used profitably for routine checking of vaporizer performance.

For the past 7 years, we have been working on the clinical application of closed-circuit anesthesia. We have found that, after initial equilibration of the desired concentration of anesthetics in the circuit and the functional residual capacity, the input anesthetic gas flow can be kept nearly constant. The supply of anesthetic agent to match patient requirements is not critical, because the large circuit volume acts as a buffer, and because uptake is concentration dependent and serves as a feedback control. Therefore, with the accuracy of vaporizer performance (except in Fluotec Mark II) that we determined in this study, one can safely perform clinical closed-circuit anesthesia.

## REFERENCES

1. Cole JR: The use of ventilators and vaporizer performance. Br J Anaesth 36:646-652, 1966
2. Whitcher CE, Piziali R, Sher, R, et al: Development and evaluation of methods for the elimination of waste anesthetic gases and vapor in hospitals. Dept of Health, Education and Welfare Publication 77-140 (NIOSH), May 1975, pp 57-137
3. Enderby GEH: Gas exhaust valve. Anaesthesia 27:334-337, 1972
4. Hill DW Lowe HJ: Comparison of concentration of halothane in closed and semiclosed circuits during controlled ventilation. Anesthesiology 23:291-298, 1962
5. Hill DW: The design and calibration of vaporizers for volatile anesthetic agents. Br J Anaesth 40:656-659, 1968

6. Edmondson W, Hill DW: A pressurizing valve for the Fluotec vaporizer. Br J Anaesth 34:741–745, 1962
7. Dorsch JA, Dorsch SE: Understanding Anesthetic Equipment. Baltimore, Williams & Wilkins Co, 1975, pp 95–97
8. Stoelting RK: The effect of nitrous oxide on halothane output from Fluotec Mark 2 vaporizers. Anesthesiology 35:215–218, 1971
9. Morgan M, Lumley J: Reliability of halothane vaporizers. Anaesthesia 23:440–445, 1968
10. Murray WJ, Fleming P: Fluotec Mark 2 halothane output: nonlinearity from "off" to 0.5 per cent dial settings. Anesthesiology 36:180–181, 1972
11. Latto IP: Administration of halothane in the 0–0.5% concentration with the Fluotec Mark 2 and Mark 3 vaporizers. Br J Anaesth 45:563–569, 1973
12. Diaz PM: The influence of carrier gas on the output of automatic plenum vaporizers. Br J Anaesth 48:387–391, 1976
13. Nawaf K, Stoelting RK: Nitrous oxide increases enflurane concentrations delivered by Ethrane vaporizers. Anesth Analg 58:30–32, 1979
14. Stoelting RK, Nawaf K: Enflurane vaporizer accuracy with nitrous oxide mixtures (letter). Anesth Analg 58:441, 1979
15. Lin C-Y: Enflurane vaporizer accuracy with nitrous oxide mixtures (letter). Anesth Analg 58:440–441, 1979

---

## Smoke Inhalation Decreases Pulmonary Surfactant

The objective of this study was to define the primary pathophysiology of acute smoke inhalation without the variables of infection, burns, or fluid resuscitation. A standard dose of smoke (wood and kerosene) was delivered at 37 C to mongrel dogs. Measurements included arterial blood gases, carboxyhemoglobin, pulmonary and systemic hemodynamics, respiratory mechanics, surface tension area curves as an indication of surfactant activity, and in vivo photomicroscopy. The $F_{IO_2}$ of the smoke was 0.17; the carbon monoxide 17,000 ppm. Immediately following smoke exposure, dense nonsegmental atelectasis developed. Hemodynamic changes were insignificant, but the$Pa_{O_2}$ decreased to 49 mm Hg; the right to left shunt increased from 5% to 41%. Surfactant reduction increased the minimum surface tension from 7 to 22 dynes/cm. This surfactant loss may explain the atelectasis and the marked instability of subpleural alveolar walls. The data suggest that acute inactivation of surfactant is one of the primary pathophysiologic events in smoke inhalation. (*Nieman GF, Clark WR Jr, Wax SD, et al: The effect of smoke inhalation on pulmonary surfactant. Ann Surg 191:171–181, 1980*)

ANESTH ANALG
59:367–370, 1980

# Hospital Admission Blood Pressure: A Predictor for Hypertension following Endotracheal Intubation

Robert F. Bedford, MD,* and Barney Feinstein, MD†

BEDFORD, R. F., AND FEINSTEIN, B.: Hospital admission blood pressure: a predictor for hypertension following endotracheal intubation. Anesth Analg 59:367–370, 1980.

An analysis of 245 consecutive general anesthetics revealed that patients who were the most likely to develop arterial hypertension after endotracheal intubation often had elevated (<140/90 torr) blood pressure (BP) at the time of hospital admission, although they were normotensive (>140/90) while on the hospital wards. The validity of this observation was tested prospectively by monitoring heart rate and intra-arterial pressure and then recording the response to endotracheal intubation in 50 consecutive patients who were divided into three groups: group I (30 patients) had BP < 140/90 torr during and after admission; group II (12 patients) had BP > 140/90 torr on admission but <140/90 torr during hospitalization; and group III (8 patients) had BP > 140/90 torr during and after admission. After rapid-sequence intubation with a thiopental-succinylcholine anesthetic technique, heart rate and rate-pressure product increased significantly in all three groups of patients. Mean BP in group 1 increased from 90 torr ± 2 SE just before induction to a peak value of 117 torr ± 5 just after intubation ($p < 0.05$). The corresponding values in group III were 118 torr ± 5 SE and 129 torr ± 9 SE, respectively ($p > 0.05$). In contrast, mean BP increased from 102 torr ± 5 SE to 152 ± 4 SE in group II ($p < 0.001$ versus control and $p < 0.05$ versus groups I and III). Two of these 12 patients developed ST-segment depression compatible with myocardial ischemia and eight required rapid reduction in BP with vasodilators and/or additional thiopental. It is concluded that the response of BP to the stress of the hospital admission serves as a predictor for identifying patients who are most prone to develop severe hypertension following endotracheal intubation, especially after a rapid induction of anesthesia.

**Key Words:** INTUBATION, Endotracheal: blood pressure; BLOOD PRESSURE: intubation.

ENDOTRACHEAL intubation in lightly anesthetized patients frequently results in arterial hypertension and tachycardia which may cause subarachnoid hemorrhage, cardiac failure,[1] or myocardial ischemia.[2] Although many preventive measures have been proposed for patients who might be at risk for developing hypertension after endotracheal intubation, the only patients heretofore identified as being likely to develop such hypertension are those in whom blood pressure is controlled poorly preoperatively.[3] The present study was undertaken in order to identify other patients who might be likely to develop marked hypertension in response to endotracheal intubation.

## Methods and Materials

### Preliminary Evaluation

A prospective evaluation of 245 consecutive general anesthetics performed for elective noncardiac operations at the University of Virginia Hospital was undertaken in 1978. In each case anesthesia was induced with thiopental and maintained with a variety of intravenous or inhalational techniques. Each anesthetist was interviewed shortly after patients underwent endotracheal intubation. Blood pressure (BP) just before induction and the first BP measured by Korotkoff sounds after intubation were tabulated, as was the general anesthetic technique employed. Each patient's hospital record was then reviewed with particular attention to BP recorded at the time of hospital admission and routine BP measurements made on the wards. Additional items sought were a history of hypertension and its treatment if any, and clinical evidence for cardiovascular disease, either from history, physical examination, or diagnostic studies. After evaluating the preoperative hospital BP records it was possible to identify three groups of patients. Group I (167 patients) had admission BP and average BP in hospital <140/90. Group II (48 patients) had admission BP >140/90 and average BP in hospital <140/90. Group III (30 patients) had admission BP and average BP in hospital >140/90. None of the patients in group I was known to be hypertensive, whereas 15 of the patients in group II had been told they were hypertensive and their condition was considered medically controlled. Twenty-one patients in group III had known hypertension for which they were receiving medication. None was thought to have a poorly controlled condition, and the group's average BP on the ward was 154 ± 3 SE/95 ± 1.7 SE.

---

* Assistant Professor.

† Resident.

Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication January 31, 1980. Presented at the 54th Congress of the International Anesthesia Research Society, March 9–13, 1980, Reno, Nevada.

Reprint requests to Dr. Bedford.

### Prospective Study of Hypertension after Endotracheal Intubation

Analysis of the preliminary data indicated that only group 2 had a statistically significant increase in mean BP after endotracheal intubation (see "Results"). To test the usefulness of preoperative hospital BP records for predicting hypertension following intubation, we then recorded intra-arterial changes in BP following endotracheal intubation in 50 consecutive informed patients who received a single anesthetic technique for major elective noncardiac operations. (The protocol for this study was reviewed and approved by the local Committee for the protection of human subjects in research.) Based on preoperative BP records as described above these patients were divided into group I, 30 patients, group II, 12 patients, and group III, 8 patients. Premedication consisted of morphine, 0.1 mg/kg IM, diazepam, 0.1 mg/kg orally, and atropine, 0.4 mg IM, 1 hour before arrival in the operating room. A 20-gauge radial arterial cannula was placed percutaneously using local anesthesia and BP was continuously transduced (Bentley "800" transducers) and recorded. Awake control heart rate (HR) and BP were determined; 100% oxygen was used for denitrogenation. After injection of gallamine, 20 mg IV, general anesthesia was induced with thiopental, 3 to 4 mg/kg IV, followed immediately by succinylcholine, 1.5 mg/kg IV. Laryngoscopy and endotracheal intubation, performed as soon as the patients became apneic, were always completed within 20 seconds. Ventilation was controlled after intubation using a tidal volume of 10 ml/kg and a rate sufficient to maintain the same end-tidal $CO_2$ fraction (Beckman LB-2) as measured before induction of anesthesia. Phasic blood pressure and standard electrocardiogram (ECG) lead II were recorded continuously, starting prior to induction of anesthesia and continuing for 5 minutes after intubation. Mean arterial pressure was calculated as diastolic pressure plus one third the pulse pressure difference, and rate-pressure product was derived from systolic pressure multiplied by heart rate.

Statistical comparisons were performed using analysis of variance and least significant difference testing. $p < 0.05$ was regarded as statistically significant.

## Results

The Figure summarizes the results of our preliminary study of 245 patients, correlating blood pressures obtained both at hospital admission and on the wards with blood pressures measured just before induction of anesthesia and just after endotracheal intubation. The patients in group II not only sustained a signifi-

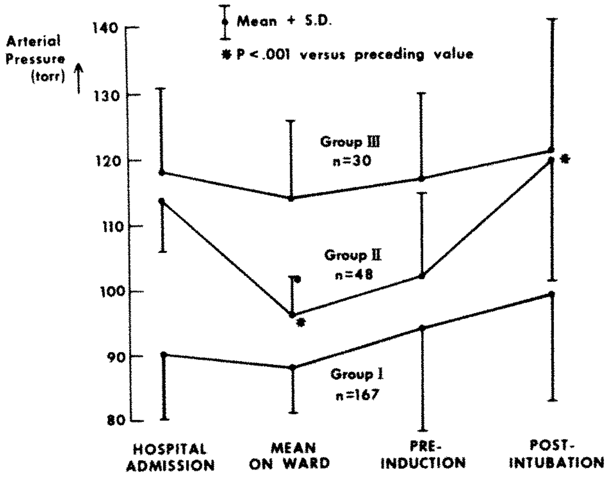


FIGURE. Mean arterial blood pressure response to hospital admission and endotracheal intubation in three groups of patients. A significant increase in blood pressure occurred following intubation only in the group of patients who were hypertensive (>140/90 torr) at the time of admission but who were otherwise normotensive during hospitalization.

cant increase in mean BP after intubation, but 15% of the patients in group II developed a peak mean BP after intubation which was 40 torr higher than their highest previously measured BP. We also sought to find a correlation between hypertension after intubation and other factors, such as the anesthetic technique used, a previous history of hypertension, or the type of medical management used for control of hypertension preoperatively. None of these variables correlated as closely with hypertension after intubation as did the hospital admission BP.

Data recorded from the 50 patients with direct arterial monitoring and rapid-sequence intubation are tabulated in the Table. The three groups of patients were similar clinically except that patients in group 3 were significantly older than were patients in groups I and II, and all were receiving antihypertensive medication. Resting heart rates were similar in all groups whereas mean arterial pressure measured just before induction of anesthesia was significantly lower in group I as compared to groups II and III. Rate-pressure product (RPP) before anesthesia was significantly higher in group III than in groups I and II.

After endotracheal intubation, heart rate and rate-pressure product increased significantly above resting values in all three groups of patients. The patients who were hypertensive before anesthesia (group III) did not have significant increases in arterial pressure after intubation. Normotensive patients (group I) had a statistically significant increase in mean arterial pressure after intubation, but none of these increases required pharmacologic intervention for BP control. In contrast, the patients in group II developed peak mean blood pressures 50 torr higher than control values, with a mean systolic/diastolic value of 214 ± 6 SE/120 ± 4 SE. Peak BP and RPP were significantly higher than values measured in groups I and III after endotracheal intubation. Additional thiopental and/or vasodilator was given promptly to control blood pressure in eight of the 12 patients in group II. Transient S-T segment depression was observed in two cases, but there were no instances of postoperative myocardial infarction or other complications related to intubation, and all blood pressures returned to control values within 5 minutes after intubation. There was no difference in cardiovascular response between the patients in group II who received preoperative antihypertensive medication and those who were untreated.

## Discussion

Elective admission to a hospital is an emotionally and physically stressful experience despite the best efforts of all personnel involved. Many patients who are normotensive during routine BP measurement on the hospital ward demonstrate elevated BP when measured as they are being admitted.[4] In the present study these patients were considered to be normotensive, although some had previously documented hypertension which responded satisfactorily to medical therapy. Our data suggest, however, that a mild hypertensive response to the stress of hospital admission, regardless of the patient's medical history, may serve to alert the anesthetist to the possibility that the patient may develop a hypertensive response to the stress of endotracheal intubation. This may reflect inadequate therapy of previously diagnosed hypertension, or it may indicate a previously unsuspected predilection toward hypertension. Peak mean rate-pressure product for the patients in group II after intubation was 20,972 ± 871 SE, a measure of myocardial oxygen demand far in excess of the 11,000 value at which Roy et al.[2] found ECG evidence for myocardial ischemia in patients with known coronary artery disease. Although none of our patients had known coronary artery disease, it is not surprising in view of the observed increase in myocardial oxygen demands that two of the 12 patients in group II developed transient S-T segment depression after endotracheal intubation. Had lead $V_5$ been monitored,

**TABLE**

**Heart Rate (HR), Mean Arterial Pressure (MAP), and Rate-Pressure Product (RPP) before and after Endotracheal Intubation in Patients with Direct Arterial Pressure Monitoring***

| Group | N | Age (years) | Awake control values | | | Peak values after intubation | | |
|---|---|---|---|---|---|---|---|---|
| | | | HR | MAP | RPP | HR | MAP | RPP |
| 1 | 30 | 46 ± 3 | 80 ± 2 | 90 ± 2† | 10,865 ± 225 | 99 ± 2‡ | 117 ± 5‡ | 16,109 ± 717‡ |
| 2 | 12 | 51 ± 4 | 76 ± 4 | 102 ± 5 | 11,769 ± 861 | 98 ± 4‡ | 152 ± 4†‡ | 20,972 ± 871†‡ |
| 3 | 8 | 63 ± 5† | 77 ± 3 | 118 ± 5 | 13,778† ± 737 | 100 ± 5‡ | 129 ± 9 | 17,033 ± 1042 |

* Values are means ± SE.

† $p < 0.05$ versus the other groups' values.

‡ $p < 0.05$ versus control values.

an even higher incidence of ischemia might have been seen.[5]

The remarkably stable BP following intubation in the hypertensive patients in group III was somewhat unexpected. During the preliminary study we felt that this was related to administration of deep levels of volatile anesthetics before intubation, but we later observed the same pattern after rapid-sequence intubation as well. Prys-Roberts et al.[3] likewise found no increase in BP over awake control measurements following intubation of patients with hypertension, but these patients were intubated only after prolonged inhalation of 1% halothane. In the present study we believe that the preoperative medical therapy of all the patients in group III was responsible for minimizing the response of their BP to intubation.

Previously diagnosed hypertensive patients who were treated medically and remained normotensive both during and after hospital admission responded to intubation in the same fashion as the other patients in group I who had no prior history of hypertension. The increase in BP for group I was essentially identical with that reported previously by Forbes and Dally[6] in normotensive patients undergoing rapid-sequence intubation. Prys-Roberts et al.[7] likewise noted that adequately treated hypertensive patients responded similarly to normotensive patients during general anesthesia.

In summary, we have described a subgroup of patients comprising about 20 to 25% of the surgical population who are prone to develop severe reactive hypertension in response to endotracheal intubation. These patients can be identified in advance because although they have normal BP following hospital admission, their BP is significantly elevated at the time of admission. When a rapid-sequence intubation is required, these are the patients who probably are most likely to benefit from pretreatment with deep levels of anesthesia[8] or adjuvants such as lidocaine,[9] phentolamine,[10] or nitroprusside.[11] Patients receiving medical therapy for moderate hypertension that is present at the time of hospital admission and that is stable following admission have no further increase in BP following intubation.

## REFERENCES

1. Fox EJ, Sklar AS, Hill CH, et al: Complications related to the pressor response to endotracheal intubation. Anesthesiology 47:524–525, 1977
2. Roy LW, Edelist G, Gilbert B: Myocardial ischemia during non-cardiac surgical procedures in patients with coronary artery disease. Anesthesiology 51:393–397, 1979
3. Prys-Roberts C, Greene LT, Melocha R, et al: Studies of anesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 43:531–547, 1971
4. Greene NM: Preanesthetic blood pressure determinations: an analysis of 12,139 cases under clinical conditions. Anesth Analg 42:454–462, 1963
5. Kaplan JA, King SB: The precordial electrocardiographic lead ($V_5$) in patients who have coronary-artery disease. Anesthesiology 45:570–574, 1976
6. Forbes AM, Dally FG: Acute hypertension during induction of anesthesia and endotracheal intubation in normotensive man. Br J Anaesth 42:618–624, 1970
7. Prys-Roberts C, Meloche R, Foex P: Studies of anaesthesia in relation to hypertension. I. Cardiovascular responses of treated and untreated patients. Br J Anaesth 43:122–136, 1971
8. King BD, Harris LC, Greifenstein FE, et al: Reflex circulation responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 12:556–566, 1951
9. Denlinger JK, Ellison N, Ominsky AJ: Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. Anesthesiology 41:409–412, 1974
10. De Vault M, Greifenstein FE, Harris LC: Circulatory responses to endotracheal intubation in light general anesthesia—the effect of atropine and phentolamine. Anesthesiology 21:360–362, 1960
11. Stoelting RK: Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 58:116–119, 1979

ANESTH ANALG
59:371-376, 1980

# Assessment of Block of the Sciatic Nerve in the Popliteal Fossa

**Duane K. Rorie, MD,* David E. Byer, MD,* David O. Nelson, MD,* Rungson Sittipong, MD,* and Kenneth A. Johnson, MD†**

---

RORIE, D. K., BYER, D. E., NELSON, D. O., SITTIPONG, R., AND JOHNSON, K. A.: Assessment of block of the sciatic nerve in the popliteal fossa. Anesth Analg 59:371–376, 1980.

Success of block of the sciatic nerve in the popliteal fossa in 130 patients was assessed by an anesthesiologist at the time of surgery. The patients were evaluated for complications by the anesthesiologist during postoperative rounds and by the orthopedic surgeon at the 1-month follow-up visit. Acceptance of the block by the patient was judged by answers on a questionnaire filled out by the patients after they had gone home. The questionnaire was designed to determine satisfaction with the block, discomfort associated with performance of the block, and whether sensations suggestive of paresthesias or other complications not evident at the time of discharge from the hospital had occurred. Of 119 patients responding to the questionnaire, 105 (88.2%) expressed overall satisfaction with the anesthesia. Two patients described sensations compatible with postoperative paresthesias, and two others described sensations that may have been paresthesias; in none did the sensations last longer than 1 month. Assessment of the blocks by the anesthesiologist in all 130 patients in the study revealed that anesthesia satisfactory for completion of the operative procedure was achieved in 107 (82.3%). General anesthesia was needed in eight patients (6.2%), and in 15 patients (11.5%) intravenous sedation or injection of the site of surgical incision with local anesthesia (or both) was needed.

**Key Words:** ANESTHETIC TECHNIQUES: Regional, sciatic block; ANATOMY, sciatic nerve.

---

BLOCK of the sciatic nerve with local anesthetics at its termination in the popliteal fossa is not used extensively for surgical procedures. The infrequent use of this block by anesthesiologists may be related to the limited area of anesthesia it provides, the possible difficulty in consistently achieving satisfactory anesthesia,[1] or the belief that blocking the sciatic nerve or its terminal branches in this location is associated with a high incidence of complications and residual paresthesias. The latter reason has been difficult to substantiate from a review of the literature. Nevertheless, a current textbook of regional anesthesia has "purposely omitted" "block procedures used infrequently, those having a high incidence of serious complications, and certain other blocks in which residual paresthesias occur with a high frequency." Included in one or more of these categories were "superficial peroneal nerve block and anterior and posterior tibial nerve block."[2]

The present study was undertaken to assess the incidence of postanesthetic complications with use of the block and to establish the overall rates of success and of acceptance by patients.

## Methods and Materials

In our practice, block of the sciatic nerve in the popliteal fossa is a standard anesthetic technique that has been used routinely for several years and is considered to be the anesthetic method of choice for operations on the foot. The major criteria for selection of this technique are (1) that the operation can be completed within the time of anesthesia provided by the block; (2) that the patient has no neurologic

---

* Consultant, Department of Anesthesiology.

† Consultant, Department of Orthopedics.

Received from the Departments of Anesthesiology and Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901. Accepted for publication January 21, 1980.

Figures 1 to 4: Copyright © Mayo Foundation.

Reprint requests to Dr. Rorie.

disease involving the lower extremity; and, (3) that no infection exists at the block site.

During collection of data for this study, an attempt was made to minimize variation in surgical techniques by including the patients operated on by only one surgeon. Thus, the criterion for inclusion in the study was that the patient receiving a block be operated on by this surgeon. Because the study involved only assessment of the success rate of the block, written informed consent by the patient for inclusion in the study was not required. The study included 130 patients operated on in a 26-month period. Information for the study was gathered on two forms. One form, filled out by the anesthesiologist at the time of surgery, included information about premedication, amount of anesthetic injected, nature of the paresthesia obtained, use of a tourniquet to provide a bloodless operative field, need for anesthetic supplementation, and adequacy of the block. The second form was a questionnaire sent to the patient 2 weeks after discharge from the hospital. The questionnaire was designed to evaluate discomfort associated with performance of the block, to determine the presence of sensations suggestive of paresthesias or other complications not evident at the time of discharge from the hospital, and to determine whether the patient was satisfied with the block.

## Patients Studied

The patients were from 14 to 84 years old (mean, 50.8 years). There were 84 females and 46 males. Operative procedures lasted from several minutes to 2 hours (average time, 51 minutes) and ranged in complexity from removal of a lipoma to multiple metatarsal osteotomies.

## Premedication

Since communication with the patient was important in successfully eliciting a paresthesia, patients were lightly premedicated: 66% received 50 mg of meperidine, 25% received 75 mg of meperidine, and 9% received no premedication. Premedication was given 30 to 45 minutes before the block procedure was begun.

## Anatomy

Popliteal fossa anatomy was reviewed by dissection in two bodies and by examining bodies dissected by medical students in 16 additional bodies.

The fossa is a diamond-shaped area located behind the knee, bounded inferiorly by the medial and lateral heads of the gastrocnemius and superiorly by the long head of the biceps femoris on the lateral side and the superimposed tendons of the semitendinosus and semimembranosus on the medial side[3] (Figs 1 to 3).

The sciatic nerve, formed from spinal cord segments L-4 through S-3, is actually two nerves contained within a common connective tissue sheath, the larger tibial division located medially and the common peroneal division located laterally in the nerve. In about 10% of cases, the two divisions remain separate, so that no single nerve is formed.[4] This variation existed in one of the bodies examined; although separated, the nerves were contained in close proximity within a common connective tissue sheath. Thus, at the apex of the popliteal fossa, where the

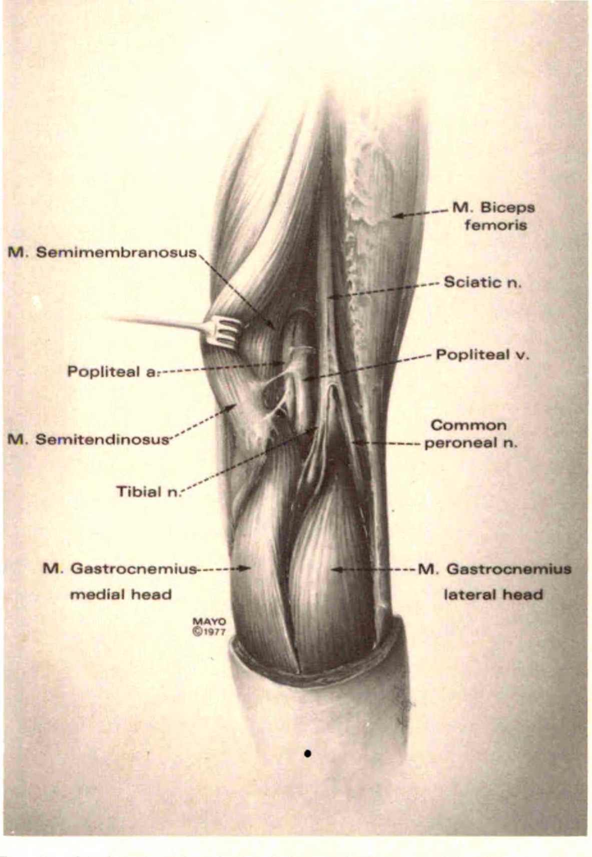


FIG 1. At the termination of the sciatic nerve in the popliteal fossa, connective tissue surrounding the nerve continues beyond its bifurcation and holds the terminal divisions in close proximity until approximately midway through the popliteal fossa. Beyond this point, lateral divergence of the common peroneal nerve places it parallel to the tendon of the biceps femoris muscle for a short distance before it leaves the fossa. Note that the sciatic nerve is slightly lateral to the midline. (Printed with permission. Copyright © 1977 Mayo Foundation.)

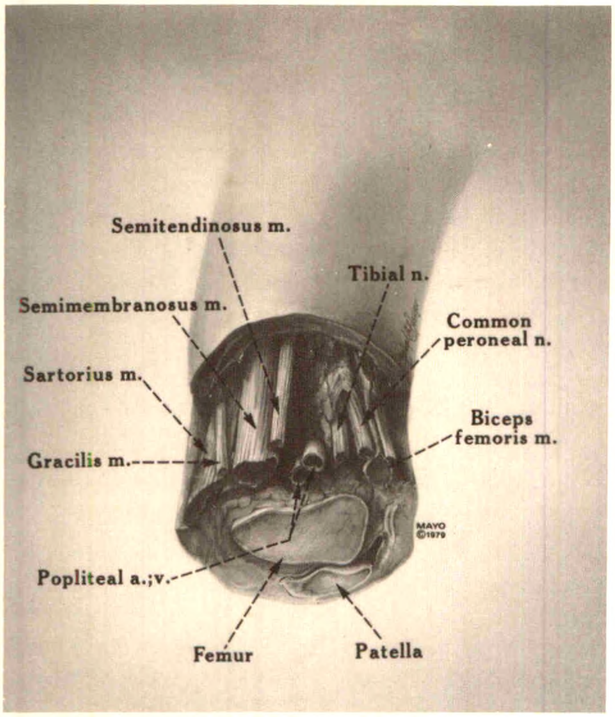


FIG 2. Cross-section of lower extremity through the popliteal fossa showing relationship of structures within the fossa. Superior medial and lateral boundaries are formed by tendons of the semitendinosus muscle and the long head of the biceps femoris muscle, respectively. The sciatic nerve is dividing into the common peroneal nerve and the tibial nerve. The femoral artery lies close to the femur, with the popliteal vein superficial to the artery. Both vessels are 1 to 1.5 cm medial to the nerves. The nerves are suspended approximately midway between the skin and the posterior surface of the femur in the fat-filled fossa (dissected away in this drawing). (Printed with permission. Copyright © 1979 Mayo Foundation.)

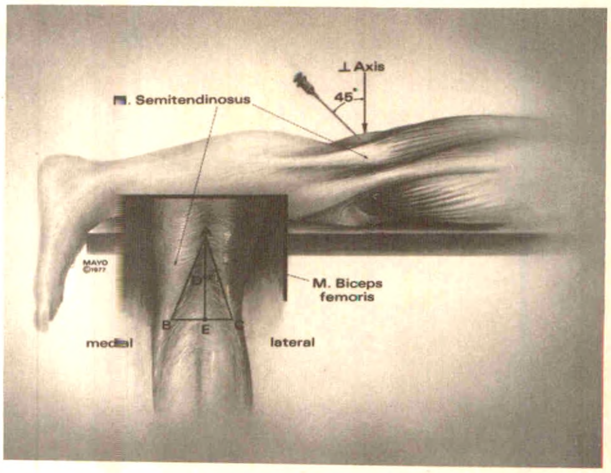


FIG 3. Upper half of the popliteal fossa is identified by palpation and is represented by triangle ABC. Line A-B corresponds to the tendon of the semitendinosus muscle; line A-C, to the tendon of the long head of the biceps femoris; and line B-C, to the skin crease in the back of the knee. Line A-E bisects the triangle into equal halves. Point D is 5 cm superior to point E. The needle is inserted at "X," 1 cm lateral to point D, at an angle of 45 to 60° to the skin and is advanced until a paresthesia is obtained. (Printed with permission. Copyright © 1977 Mayo Foundation.)

sciatic nerve typically terminates by dividing into common peroneal and tibial parts (Fig 1), the ununited divisions were in approximately the same relation as they are when a single sciatic nerve is formed.

After the sciatic nerve terminates, the components are held in close proximity for an additional 1 to 3 cm by the surrounding connective tissue sheath, so that the lateral divergence of the common peroneal nerve in its course through the popliteal fossa is gradual. The tibial nerve continues in the same direction as the sciatic and is parallel to and 0.5 to 1 cm lateral to the midline of the popliteal fossa (Figs 1 and 3).

Because the popliteal fossa is filled with fat, diffusion of injected local anesthetics may be impaired. Positioning the needle tip near the nerve before injection enhances the chance of a successful block. The position of the needle should be confirmed by eliciting a paresthesia. Understanding the relationships of the nerves within the fossa helps in positioning the needle. It is particularly important to know that the sciatic nerve and its terminal branches are superficial to the popliteal vessels and are located approximately midway between the posterior surface of the femur and the skin covering the fossa (Fig 2). The distance from nerve to skin or from nerve to posterior surface of the femur is usually between 1.5 and 2 cm. Remembering the intermediate position of the nerve is important if a paresthesia is not obtained with the first thrust of the needle, since the needle can be pivoted over the nerve when the direction is changed. Therefore, the tip of the needle should be brought to the surface of the skin before the needle is redirected.

The common peroneal nerve, after leaving the popliteal fossa, winds around the neck of the fibula and divides into deep and superficial peroneal nerves. The tibial nerve leaves the popliteal fossa and runs deep in the leg in company with the posterior tibial artery to a point between the medial malleolus and the calcaneus, where it divides into medial and lateral plantar nerves. The distribution of these nerves is shown in Fig 4. The sural and saphenous nerves also contribute to the cutaneous innervation of the leg and foot (Fig 4). The sural nerve is formed chiefly from the tibial nerve, but it also receives fibers from the common peroneal; the saphenous nerve is a branch of the femoral.

### Block Technique

The patient, in the prone position, is asked to lift (flex) his leg about 30° from the table top. This maneuver causes the upper borders of the popliteal fossa to become more easily palpable. The upper borders are then outlined, and the popliteal fossa is divided into equal medial and lateral triangles (Fig 3). An intradermal wheal of local anesthetic is raised approximately 5 cm superior to the skin crease behind the knee joint (line B-C) and 1 cm lateral to point D on the line (A-E) that bisects the superior part of the popliteal fossa (Fig 3). A 22-gauge, 7.5-cm spinal needle is introduced through the wheal while being held at an angle of 45 to 60° to the skin, with the tip in an anterior and superior direction. The needle is advanced until a paresthesia is obtained. The needle is then withdrawn 1 to 2 mm to minimize the possibility of intraneural injection. After aspiration with the syringe, 35 to 45 ml of equal volumes of 0.5% bupivacaine and 3% chloroprocaine is injected (approximately 0.5 to 0.6 ml/kg of body weight in adults; the block is not used in pediatric patients).

If an Esmarch tourniquet is placed above the ankle to achieve a bloodless field (done in all but one patient in this study), a saphenous nerve block is performed in addition to the previously described block. This is done by injecting 5 to 10 ml of the anesthetic mixture deeply subcutaneously in a 5-cm arc just below the medial surface of the tibial condyle.

The entire block procedure can be done in less than 10 minutes. Anesthesia is sufficiently complete to permit surgery to begin in 25 to 35 minutes.

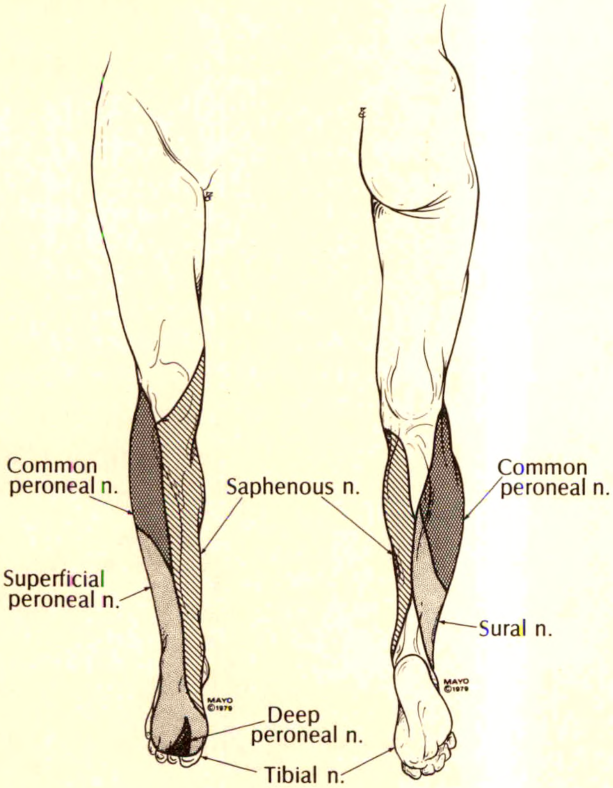


FIG 4. Area of peripheral distribution of cutaneous nerves of the leg: anterior view (left) and posterior view (right). (Printed with permission. Copyright © 1979 Mayo Foundation.)

## Results

### Evaluation of Blocks by Anesthesiologists

Anesthesia satisfactory to complete the entire operation was achieved in 107 patients (82.3%). The remaining 23 patients (17.7%) needed additional anesthesia at some point during surgery (Table 1). In four patients (3.1%), tourniquet pain developed about 1 hour after the operation had begun; they were given diazepam (2.5 to 10 mg), meperidine and promethazine (Mepergan) (0.25 to 2 ml), or fentanyl and droperidol (Innovar) (1 to 2 ml). Five patients (3.8%) were aware of the surgical incision; after injection of 2 to 5 ml of 1% lidocaine at the site of the incision, the surgical procedure was completed without discomfort. In six patients (4.6%), anesthetic infiltration of the incisional site by the surgeon and supplementary sedation by intravenous administration of drugs were needed. Eight patients (6.2%) received general anesthesia.

### Evaluation of Blocks by Patients

The questionnaire assessing discomfort experienced during performance of the block, overall satisfaction with the block, and any complication occurring after dismissal from the hospital was returned by 119 patients (91.5%). The discomfort associated with

TABLE 1

**Patients Receiving Block and Those Requiring Additional Anesthesia**

| | Patients | |
|---|---|---|
| | No. | % |
| Receiving block | 130 | |
| Requiring additional anesthesia | 23 | 17.7 |
| Local anesthetic injected by surgeon | 5 | 3.8 |
| Intravenous sedation (diazepam, Mepergan, or Innovar) | 4 | 3.1 |
| Both local anesthetic and intravenous sedation | 6 | 4.6 |
| General anesthesia | 8 | 6.2 |

the block procedure, summarized in Table 2, was found to be minimal ("Hardly hurt") by 56 patients (47.1%), mild ("Not too bad") by 32 (26.9%), moderate ("Significant pain, but acceptable") by 26 (21.8%), and severe ("It was awful") by 5 (4.2%). Table 3, a summary of overall satisfaction, shows that 89 of the 119 responding patients (74.8%) were completely satisfied with the anesthesia, 16 (13.4%) were satisfied but had minor reservations, 3 (2.5%) were satisfied but had major reservations, 9 (7.6%) were dissatisfied, and 2 (1.7%) did not answer the question.

### Complications Associated with Blocks

No hematomas or infections were found during the postoperative visit or during the 1-month follow-up visit to the orthopedics clinic, nor were these complications reported in any questionnaire. No paresthesias had been noted by any patient by the time the postoperative visit was made. In the questionnaire, however, two patients clearly described sensations compatible with paresthesias, and two others described sensations that may have been paresthesias. In all four patients, the frequency and intensity of the sensations likely to have been paresthesias decreased before disappearing at about 1 month.

## Discussion

This study indicates that block of the sciatic nerve and its terminal branches in the popliteal fossa can be used to provide anesthesia for short surgical procedures involving the ankle and foot. The technique is simple; it involves eliciting a paresthesia in the distribution of either the common peroneal or the tibial nerve and depositing local anesthetic around the site of paresthesia. Thus, placement of the local anesthetic solution around the nerve trunk is assured. A paresthesia was usually not difficult to elicit except in grossly obese patients. Since a paresthesia is essential to correct placement of the drug and a successful block, a peripheral nerve stimulator[5] is useful in patients in whom paresthesias are difficult to obtain. Although not used in any of the patients in this study, this aid is used now whenever difficulty is encountered in eliciting a paresthesia.

The block provided anesthesia adequate for surgical procedures lasting up to 120 minutes, although the average operative time was 51 minutes. Eight (6.2%) of 130 patients receiving the block required general anesthesia before the surgical procedure could be completed. Among the eight patients, however, was one whose operation, because of a scheduling problem, was delayed for 120 minutes after completion of the block. Although this patient had good anesthesia and tolerated the procedure well at the beginning of the operation, general anesthesia supplementation had to be given to complete the surgical procedure. This event, although causing the incidence of patients requiring general anesthesia to be higher by one patient than it realistically should have been (6.2% instead of 5.4%), suggests that with the volume and concentration of local anesthetics used, anesthesia exceeding 2.5 hours may not predictably result.

Since communication with the patient is important in successfully eliciting a paresthesia, the patients were lightly premedicated, a factor that undoubtedly increased the incidence of discomfort associated with performance of the block.

Sensations probably representing postoperative paresthesias were reported by four patients (3.4%). The onset was not noted until several days after the operation and seemed to coincide with the reestablishment of weight bearing during ambulation. The cause of these sensations is unknown, but they could have been due to the operative procedure, to the tourniquets that were used, or to the anesthetic procedure. In all patients, the sensations had disappeared by the time of the 1-month follow-up visit.

The results of this study, differing from those of a previous report that suggested satisfactory anesthesia

**TABLE 2**

**Discomfort Associated with Block Procedure Reported by 119 Patients Returning Questionnaire**

| | Patients | |
|---|---|---|
| | No. | % |
| Minimal: "Hardly hurt" | 56 | 47.1 |
| Mild: "Not too bad" | 32 | 26.9 |
| Moderate: "Significant pain, but acceptable" | 26 | 21.8 |
| Severe: "It was awful" | 5 | 4.2 |
| Total | 119 | 100 |

**TABLE 3**

**Overall Satisfaction with Anesthesia Expressed by 119 Patients Returning Questionnaire**

| | Patients | |
|---|---|---|
| | No. | % |
| Completely satisfied | 89 | 74.8 |
| Satisfied with minor reservations | 16 | 13.4 |
| Satisfied with major reservations | 3 | 2.5 |
| Dissatisfied | 9 | 7.6 |
| Did not answer this question | 2 | 1.7 |
| Total | 119 | 100 |

is difficult to achieve with this block,[1] suggest that block of the sciatic nerve at its termination in the popliteal fossa or block of its terminal branches arising there is not associated with a high incidence of serious complications and residual paresthesias. Further, the block was well accepted by patients.

## REFERENCES

1. Bryce-Smith R: Local analgesia of the limbs. Monogr Anaesth 5:70, 1976
2. Moore DC: Regional Block: A Handbook for Use in the Clinical Practice of Medicine and Surgery. Fourth edition. Springfield, IL, Charles C Thomas, Publisher, 1965, p vii
3. Woodburne RT: Essentials of Human Anatomy. Sixth edition. New York, Oxford University Press, 1978, p 533
4. Larsell O: The nervous system, in Morris' Human Anatomy: A Complete Systematic Treatise. Tenth edition. Edited by JP Schaeffer. Philadelphia, Blakiston Co, 1942, p 1133
5. Montgomery SJ, Raj PP, Nettles D, et al: The use of the nerve stimulator with standard unsheathed needles in nerve blockade. Anesth Analg 52:827-831, 1973

---

## Negative Inotropic Effect of Albumin

The inotropic effects of albumin were studied in 94 seriously injured patients who received an average of 14.5 transfusions, 9.2 L of crystalloid, and 0.9 L of plasma prior to the end of surgery. By random selection, 46 patients received added albumin averaging 31 g during surgery, 198 g during the early postoperative period, and 395 g during the next 4 days. Left ventricular stroke work index, (LVSWI) was plotted against pulmonary wedge pressure (PWP) in 22 patients who had indwelling thermistor pulmonary artery catheters at the time of the first study. Calculated heart work units (WU) were derived from the pulse pressure, mean arterial pressure, pulse rate, and central venous pressure (CVP) in patients without LVSWI measurements. Albumin supplementation increased serum albumin (4.2 vs 2.9 g%), plasma volume, CVP (15 vs 9 cm $H_2O$), but did not alter red cell volume (1531 vs 1519 ml). The ratio of LVSWI/PWP fell in albumin patients (1.9 ± 1.6 vs 4.8 ± 1.8), and the ratio of WU/CVP was significantly depressed in the albumin group (4.9 ± 2.3 vs 7.3 ± 2.1). The slopes of the LVSWI/PWP and WU/CVP were shifted to the right the albumin group. This negative inotropic effect was associated with impaired oxygenation, as reflected by an increased ratio of inspired oxygen to arterial oxygen tension (0.62 ± 0.06 vs 0.33 ± 0.1). Finally, 24 of the 46 albumin-treated patients were digitalized for heat failure, compared to only 11 of the patients who did not receive albumin. These data suggest that albumin should be considered a potentially negative inotropic agent. (*Dahn MS, Lucas CE, Ledgerwood AM, et al: Negative inotropic effect of albumin resuscitation for shock. Surgery 86:235–241, 1979*)

CLINICAL reports

# Human Malignant Hyperthermia: Awake Episodes and Correction by Dantrolene

**Gerald A. Gronert, MD,**
**Rodney L. Thompson, MD, and**
**Burton M. Onofrio, MD**

One of the remarkable differences between human and porcine malignant hyperthermia (MH) is that MH in swine may be easily triggered by stress in awake animals but that human MH has generally been observed only during anesthesia. The report of Wingard and Gatz[1] of a higher incidence of unexplained deaths in susceptible families suggests that episodes of MH in awake humans may not be rare. These episodes might, however, be more subtle in humans than in swine, in that humans may learn to regulate their environment so as to restrict the initiating or contributing factors. The following case report of episodic hyperthermia may be an example of human MH triggering while awake.

## Case Report

A 42-year-old man requested examination because of an intermittent fever of unknown origin. Approximately 20 to 25 years previously, he had first noted that extreme physical or emotional stress or fatigue resulted in aching in his joints, malaise, fever to 40 C or more, and soaking sweats. These signs and symptoms persisted despite treatment with aspirin and surface cooling. After 3 to 4 days, the fever finally "broke," leaving him exhausted and requiring several days of rest. Prior examinations from other hospitals document these episodes; their findings were otherwise negative, however, except for both a mildly elevated blood sugar and diabetic glucose tolerance test during the episodes only. He had not been exposed to anesthetic agents that trigger MH. Over the years the patient had learned to prevent or limit these episodes by avoiding stress or fatigue and by the occasional use of diazepam and aspirin. Upon examination the patient was muscular, slightly obese, and 175 cm tall; he weighed 90 kg and had appropriate strength. Physical examination and laboratory data were within normal limits.

Because his episodes resembled those of malignant hyperthermia, further work-up included stressed cardiac examination, electromyography, platelet count and morphology, red cell fragility, serum creatine phosphokinase (CPK) level, and muscle biopsy with halothane-caffeine contracture dose-response curves and measurements of adenosine triphosphate (ATP) depletion. All were within normal limits, except for the contracture responses.

The muscle biopsy was performed using 1% procaine local infiltration and bundles were prepared as previously described.[2,3] One bundle was placed in a caffeine bath; it was 1.2 cm long with wet weight of 0.0791 g. Another bundle was placed in a halothane-caffeine bath; it was 1.4 cm long and weighed 0.0832 g. Both bundles were stimulated supramaximally at 8 msec and 0.1 Hz, optimal length ($l_O$) was determined, and the bundles were then allowed to stabilize for 20 minutes in the 37 C baths. Caffeine baseline tension was 1.20 g and halothane baseline tension was 1.40 g. No contracture developed with halothane alone. Caffeine contracture responses (Figure) were shifted to the left as compared to those from normal patients.[2] The differences in $l_O$ (0.3 for the patient vs 0.2 for the normal group) are not responsible for the shifts in threshold, as similar variations in $l_O$ have been observed in other diagnostic evaluations that were not associated with a shift in threshold. In the ATP depletion test, ATP was 2.67 μmol/g in muscle not exposed to halothane, and 2.58 μmol/g in halothane-exposed muscle.

The patient returned home and subsequently experienced on two occasions the characteristic signs and symptoms that usually progressed into a febrile episode. The first time, he described it as ". . . the old symptoms . . .,"

---

Supported in part by grant GM 21729, National Institutes of Health, Public Health Service.

Received from the Departments of Anesthesiology, Internal Medicine, and Neurosurgery, Mayo Medical School, Rochester, Minnesota 55901. Accepted for publication November, 8, 1979.

Reprint requests to Dr. Gronert, Department of Anesthesiology.

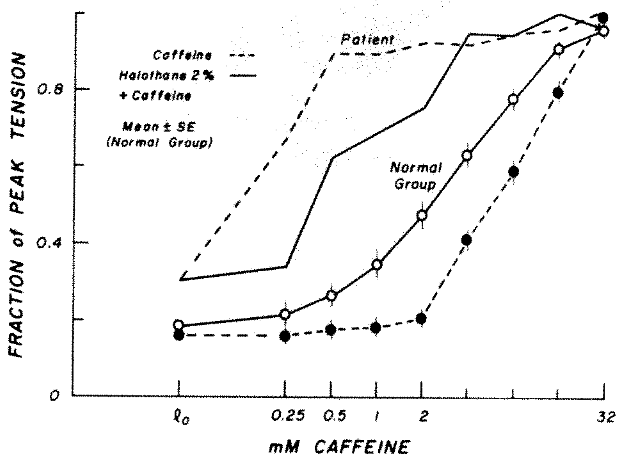


FIGURE. Contracture dose-response curves of the patient's muscle compared to mean dose-response curves from a normal population.[2] Note the shift to the left, indicating a lower threshold to caffeine in the presence or absence of halothane. $l_O$, Optimal length.

and, after several days, took dantrolene orally. It "... worked almost immediately ..." and "... any symptoms concerning a possible temperature disappeared ..." completely within 18 hours of beginning dantrolene. The initial dose was 1.1 mg/kg, and the total dose over 15 hours was 2.2 mg/kg. Several hours after beginning dantrolene, he noted weak legs, a "funny" sensation in his muscles, and loss of coordination. The second occasion was about 1 year later: "Last week the old feeling returned and I took dantrolene for the second time since the MH was uncovered. This time I reduced the dosage and took two pills at the inception. They gave me a weak feeling, but did the job just great .... All MH symptoms were relieved within 2 to 3 hours after taking the two pills." The dose was 1.1 mg/kg.

The patient's father is also muscular and has consistently elevated serum CPK values, occasionally 10 to 20 times normal levels. He did not consent to further examination. He has had three uneventful anesthetics, two without exposure to triggering agents and one that included a succinylcholine infusion for 30 minutes as a supplement to nitrous oxide and thiopental. The patient's 21-year-old daughter and 23-year-old son were evaluated and had normal CPK values and normal contracture responses on muscle biopsies. The daughter had an enflurane-succinylcholine anesthetic and the son halothane in the past, both uneventfully.

We concluded that the patient and his father are susceptible to MH and should wear Medic-Alert bands warning of the potential hazards of potent volatile agents and succinylcholine.

## Discussion

The symptoms of our patient strongly suggested a hypermetabolic response to stress, a diagnosis also proposed by another physician in 1974. The temporary diabetic pattern was apparently secondary to increased circulating levels of catecholamines or to adrenocortical stimulation, as there is a pronounced stimulation of the sympathetic nervous system during MH episodes which includes increases in circulating catecholamines to levels greater than 20 ng/ml.[4] The muscle contracture responses were decidedly abnormal for our laboratory[2] and indicate susceptibility to malignant hyperthermia.[3] ATP depletion values did not confirm the diagnosis of susceptibility; however, these have not been as accurate, in our experience, as contracture responses in determining susceptibility.[3] This patient was also unusually sensitive to dantrolene; oral doses of 2 to 4 mg/kg of dantrolene used preoperatively in several other susceptible patients have not resulted in weakness.

We conclude that MH in humans, as in swine, can be triggered in awake subjects, but that, unlike swine, humans may limit the incidence or the severity of these episodes through conscious control of their environment or emotions. Therefore, these episodes may not always be obvious to others, and the associated sympathetic hyperactivity could lead to erratic behavior or cardiac abnormalities.[5,6] These episodes could in part account for the observations of Wingard and Gatz[1] that the incidence of sudden unexplained demise is higher in MH families than in normal families.

### REFERENCES

1. Wingard DW, Gatz EE: Some observations on stress susceptible patients, in Second International Symposium on Malignant Hyperthermia. Edited by JA Aldrete, BA Britt. New York, Grune & Stratton, 1978, pp 363–372
2. Gronert GA: Contracture responses and energy stores in quadriceps muscle from humans age 7–82 years. Hum Biol 52:43–51, 1980
3. Gronert GA: Muscle contractures and adenosine triphosphate depletion in porcine malignant hyperthermia. Anesth Analg 58:367–371, 1979
4. Gronert GA, Milde JH, Theye RA: Porcine malignant hyperthermia induced by halothane and succinylcholine. Anesthesiology 44:124–132, 1976
5. Buell JC, Eliot RS: The role of emotional stress in the development of heart disease. JAMA 242: 365–368, 1979
6. Huckell VF, Staniloff HM, Britt BA, et al: Cardiac manifestations of malignant hyperthermia susceptibility. Circulation 58: 916–925, 1978

ANESTH ANALG
59:379-383, 1980

# Mitral Valve Prolapse

**Evan M. Krantz, MD,* John F. Viljoen, MD,† Robert Schermer, MD,‡ and Marcos S. Cañas, MD§**

Arrhythmias during surgery frequently confront the anesthesiologist. The type of arrhythmia can usually be ascertained by examination of the ECG; the underlying cause, however, may not be easy to determine. Surgical stimulation in an inadequately anesthetized patient, instrumentation of the airway, hypoxia, hypercarbia, electrolyte imbalance, and myocardial ischemia account for the majority of arrhythmias and should always be excluded as possible etiologic factors. An unusual cause for intraoperative arrhythmias in a previously asymptomatic patient is prolapse of the mitral valve (Barlow's syndrome).

## Case Reports

### Case 1

A 51-year-old woman was scheduled for an ovarian cystectomy. There was no history of cardiac or respiratory disease. Past history included an appendectomy performed under general anesthesia 18 months previously. The anesthesia was reportedly uneventful.

Preoperative examination revealed a healthy middle-aged woman. The heart rate was 78 beats per minute and regular, and the blood pressure was 130/80 mm Hg. The chest was normal on auscultation. The ECG and chest x-rays were within normal limits. Laboratory data included serum sodium 140 mmol/L, potassium 3.8 mmol/L, blood urea nitrogen 2.32 mmol/L, and hematocrit 38%.

The patient was given 10 mg of morphine, 25 mg of promethazine, and 0.4 mg of atropine intramuscularly 1 hour prior to arriving in the operating room. While ECG electrodes and blood pressure cuff were being attached and the intravenous infusion started, the patient developed ventricular bigeminy. Before any therapeutic intervention could be initiated, sinus rhythm resumed. The arrhythmia was ascribed to anxiety causing catecholamine release and it was decided to continue with the operation.

Anesthesia was induced with 200 mg of thiopental followed by 100 mg of succinylcholine to facilitate endotracheal intubation. Immediately upon inserting the laryngoscope, the patient once again developed bigeminy. On this occasion, instrumentation of the airway in the presence of inadequate anesthesia was presumed to be the precipitating factor. Anesthesia was rapidly deepened with a 50% mixture of nitrous oxide in oxygen and 4% enflurane; within 2 minutes a normal sinus rhythm was restored.

Anesthesia was maintained with a 50:50 nitrous oxide/oxygen mixture (total flow 6 L/min) and 2% enflurane. Satisfactory muscle relaxation was obtained with 3 mg of pancuronium. The tidal volume was 600 ml delivered at a rate of 12 breaths per minute.

Anesthesia was uneventful for approximately 45 minutes, when for the third time and without apparent reason, ventricular bigeminy recurred. Vital signs were otherwise stable and 75 mg of lidocaine was administered—without effect. Four minutes later, sinus rhythm spontaneously resumed. The operation was completed 30 minutes later.

Following 2.5 mg of neostigmine and 1.2 mg of atropine, the patient began breathing spontaneously with a vital capacity of 900 ml. On request, she opened her eyes and lifted her head. The endotracheal tube was removed and during this maneuver a fourth and equally transitory episode of ventricular bigeminy occurred.

In the recovery room, the patient was given $O_2$ at 4 L/min by nasal catheter. Bigeminy was noted to appear and disappear intermittently. Serum electrolyte levels at that time included sodium 138 mmol/L and potassium 3.8 mmol/L; an arterial blood sample showed the pH to be 7.38, $P_{O_2}$ 375 mm Hg, $P_{CO_2}$ 35 mm Hg, and a base deficit of 2.0 meq/L. A lidocaine infusion at a rate of 2 mg/min was started but the patient continued to have intermittent runs of ventricular bigeminy for some 18 hours after the operation. The anesthesiologist felt that the case merited further investigation and on the following day an echocardiogram was performed. A classic mitral valve prolapse was discovered. The patient was discharged on the 5th postoperative day, continuing to have short runs of bigeminy, although not complaining of palpitations. No medication was prescribed on discharge from the hospital.

### Case 2

A 30-year-old white man had a 7-year history of a cervical lipoma. In the past the patient had undergone an initial resection of the lipoma with laminectomy, followed by three additional operations at another institution for

---

* Assistant Professor, Department of Anesthesiology UCLA School of Medicine; Staff Anesthesiologist, Veterans Administration Wadsworth Medical Center.

† Professor of Anesthesiology, UCLA School of Medicine; Chief, Anesthesia Service, Veterans Administration Wadsworth Medical Center.

‡ Resident in Anesthesiology, UCLA School of Medicine.

§ Assistant Professor, Department of Anesthesia, UCLA School of Medicine; Staff Anesthesiologist, Veterans Administration Wadsworth Medical Center.

Received from the Anesthesia Service, Veterans Administration Wadsworth Medical Center, Wilshire and Sawtelle Boulevards, Los Angeles, California 90073. Accepted for publication December 31, 1979.

Reprint requests to Dr. Viljoen.

recurrence of the lipoma and development of arachnoiditis. As far as could be ascertained there were no anesthetic complications. The patient was admitted to UCLA Medical Center with a 3-month history of progressive upper and lower extremity weakness and urinary and fecal incontinence. A preoperative myelogram demonstrated recurrence of the lipoma. Past medical history was remarkable only for a heart murmur which the patient had been told was of no significance. The patient denied any history of palpitations, shortness of breath, or chest pain. Physical examination revealed a well-developed, well-nourished man with mild muscle wasting in both upper and lower extremities. On auscultation of the chest, a grade 2/6 midsystolic crescendo-decrescendo murmur was heard along the left sternal border and scattered expiratory wheezes were present throughout both lung fields. Admission laboratory data and preoperative chest x-ray were within normal limits. The only ECG abnormality was a somewhat short PR interval (0.11 to 0.12 seconds). The patient was premedicated with meperidine (75 mg) and promethazine (12.5 mg) intramuscularly. He was extremely anxious upon arrival in the anesthesia induction room and was given an additional 100 mg of meperidine in divided doses intravenously during insertion of an arterial catheter. Anesthesia was induced with thiopental (200 mg). Pancuronium (7 mg) was given to facilitate endotracheal intubation. Anesthesia was maintained with oxygen, nitrous oxide, and 2% enflurane. The patient was placed in a sitting position for the cervical laminectomy. Approximately 30 minutes after the operation was started the patient developed a sinus tachycardia of 140 beats per minute. Arterial blood pressure remained unchanged. It was thought that there might be a ventilatory problem and an arterial blood sample was obtained which showed pH 7.36, $P_{CO_2}$ 40 mm Hg, and $P_{O_2}$ of 135 mm Hg with $F_{IO_2}$ of 0.3. During the next 30 minutes the heart rate increased to 150 beats per minute. Close examination of the ECG revealed supraventricular bigeminy with pulsus alternans. The arterial pressure remained stable so no additional treatment was initiated. Approximately 20 minutes later atrial flutter occurred with an atrial rate of approximately 280 per minute and a ventricular rate of approximately 140, i.e., a 2:1 block. This persisted without evidence of hemodynamic compromise. It was thought that the enflurane might have contributed to the arrhythmia and so it was discontinued. Four 50-mg doses of meperidine were given intravenously over the next 20 minutes without change in rhythm. After another 20 minutes, the rhythm changed to atrial fibrillation with a ventricular response of approximately 130 beats per minute. Once again, the arterial pressure remained unchanged. For the remainder of the operation atrial fibrillation alternated with atrial flutter. At the completion of the surgery it was decided to reverse the effects of the muscle relaxant without prior treatment with atropine. Neostigmine (1.0 mg) was given intravenously. This increased the degree of block to 4:1. Reversal of neuromuscular blockade was incomplete so 0.4 mg of atropine and a another 1.0 mg of neostigmine were administered. The trachea was extubated in the operating room and before any decision could be made regarding the treatment of the arrhythmia, sinus rhythm returned. In the recovery room a 12 lead electrocardiogram was unchanged from the preoperative tracing. The patient, when interviewed on the first postoperative day, reluctantly admitted to the occurrence of palpitations but had thought that if he had volunteered this information the operation would be postponed. Physical examination at this time confirmed the 2/6 murmur heard preoperatively along the left sternal border. The murmur increased in intensity with hand squeezing and a Valsalva maneuver. When the patient squatted and then stood the click was clearly heard preceding the murmur.

## Discussion

It is only recently that a midsystolic click followed by a late systolic murmur has been identified with mitral valve prolapse. Prior to 1963 the significance of these findings was not well understood. In 1913, Gallavardin[1] ascribed them to pleuropericardial adhesions later found at autopsy. This was accepted until 1961 when Reid[2] suggested that the origin of these sounds lay in the mitral valve. In 1913, Barlow et al[3] demonstrated by angiography late systolic prolapse of the posterior leaflet of the mitral valve in patients with the click murmur.

Mitral valve prolapse is among the most common of congenital heart abnormalities. O'Rourke et al[4] estimated it to be present in 5% to 10% of the general population. The anesthesiologist may encounter the condition in three types of patients: (1) those with documented mitral valve prolapse, who are to undergo surgery for the insertion of a pacemaker to control associated bradyarrhythmias, or replacement of the mitral and one or more other heart valves; (2) those with undiagnosed mitral valve prolapse undergoing a surgical procedure unrelated to cardiac problems who develop an intraoperative arrhythmia and; (3) those who sustain an unexplained cardiac arrest which subsequently is shown to be associated with prolapse of the mitral valve.

Mitral valve prolapse has been described in all age groups. When diagnosed early in life there is a preponderance of 2 to 1 female patients. With advancing years the abnormality is equally divided between the sexes. The reason for this is unknown. Thin people seem to be more commonly affected, but there are numerous other conditions that are thought to be associated with this valvular lesion (Table 1).[5–7]

The majority of patients are asymptomatic. Those with symptoms complain of dyspnea, poor effort tolerance, and palpitations. Interestingly, during long-term monitoring, the correlation between palpitations and ECG evidence of arrhythmias is poor. Chest pain is not common, but when it occurs it does not resemble angina pectoris, nor is it relieved by nitroglycerin. The pain may be severe and last several hours. It is believed to be due to a decrease in the ratio between oxygen supply and demand in the mitral valve apparatus. Auscultation of patients with mitral valve prolapse typically reveals a midsystolic click immediately followed by a murmur with a crescendo character which may continue beyond the aortic component of the second heart sound. If the murmur is holosystolic, it signifies severe mitral incompetence. The sounds are best heard in the left decubitus position and occasionally may only be heard in this position. Occasionally the click may be absent and sometimes multiple clicks are heard. If the patient sits up, the click occurs earlier and the murmur lasts longer. The click and murmur are enhanced by the inhalation of amyl nitrate. This is thought to be due to a reduction in the heart size which allows the ventricular cavity to become smaller and the valve to prolapse earlier. Electrocardiographic abnormalities occur in up to two thirds of patients with mitral prolapse. In one third of these individuals, the T waves are flattened or inverted in leads 2, 3, and AVF. These may be mistaken for ischemic changes. Slightly less frequent are ventricular premature beats which may be multifocal in nature and demand immediate therapeutic intervention. Supraventricular tachycardia also occurs and episodes of ventricular tachycardia have been reported. The mechanism of the electrocardiographic abnormalities is unknown although some patients demonstrate a Wolff-Parkinson-White type preexcitation.

The complications of mitral valve prolapse are listed in Table 2. Arrhythmias, the most common complication, are potentially the most serious. Winkle et al,[8,9] for example, reported seven patients with mitral valve prolapse with life-threatening ventricular arrhythmias. Four of the seven had coronary angiograms and none had evidence of coronary disease. Sudden death has been ascribed to severe tachyarrhythmia although other mechanisms have been invoked, including sinus arrest. Koch and Hancock[10] reported 40 symptomatic patients with mitral valve prolapse with marked ECG changes. Over a 10-year period, 13% suffered sudden and unexplained death. Leichtman et al[11] reported a family of 11 members, seven of whom had resting heart rates below 50 beats per minute. Of these seven, five had mitral valve prolapse by echocardiography and three suffered recurrent syncopal attacks. The authors concluded that sudden death in association with mitral valve prolapse may be due to sinus arrest without ventricular escape.

Buda et al[12] proposed that coronary spasm is a possible mechanism of sudden death in patients with mitral valve prolapse based on a review of 745 patients who had coronary angiograms with a history of ischemic heart disease. Ten patients had clear evidence of coronary artery spasm during angiography and nine of these had mitral valve prolapse.

The existence of a relationship between mitral valve prolapse and coronary heart disease is controversial. Significant coronary disease has been found in 5% of patients with mitral valve prolapse studied by coronary angiography for evaluation of chest pain. This finding is not greater than could be accounted for by chance. Imazaizumi et al[13] postulated that emboli from the diseased mitral valve to the coronary arteries could occur causing ischemia of the mitral valve apparatus.

Before exploring the anesthesia implications of mitral valve prolapse, it should be emphasized that it is unknown whether the valve prolapses at all times or only when there are changes in ventricular volume or configuration. In addition, whether the arrhythmias are caused by the prolapse, or whether the prolapse is secondary to an arrhythmia which initiates a ventricular contraction before the chamber is adequately filled, is not clearly established.

When confronted by a patient with documented

**TABLE 1**

**Conditions Associated with Mitral Valve Prolapse**

- Absence of the normal dorsal thoracic kyphosis and other bony abnormalities such as kyphoscoliosis and pectus excavatum
- Marfan's syndrome
- Myxomatous degeneration of cardiac valves
- Following blunt trauma to the thoracic cage
- Rheumatic valvulitis
- Atrial septal defect
- Idiopathic hypertrophic subaortic stenosis
- Congestive cardiomyopathy
- Periartertis nodosa
- Coronary artery disease
- Tricuspid valve prolapse

**TABLE 2**

**Complications of Mitral Valve Prolapse**

- Arrhythmias (some life-threatening in nature)
- Sudden death
- Endocarditis
- Rupture of mitral chordae tendinae
- Mitral valvular incompetence

mitral valve prolapse, the anesthesiologist should be aware of the possibilities of intraoperative arrhythmias and acute mitral regurgitation. It has been repeatedly demonstrated that the prolapse of the valve is worsened by emptying the heart as with assumption of the upright posture, performance of a Valsalva maneuver, or inhalation of amyl nitrate. Sympathetic overactivity, by increasing cardiac emptying may similarly cause prolapse of the mitral valve. Preoperative medication should be generous enough to prevent anxiety with subsequent catecholamine release. Atropine is best withheld as its positive chronotropic and inotropic effects increase cardiac emptying. Every effort should be made to eliminate factors known to increase myocardial irritability, e.g., hypercarbia, hypoxemia, electrolyte disturbances (hypokalemia), and anesthetics that are associated with catecholamine release or that are prone to cause arrhythmias. Cyclopropane and ketamine are thus to be considered unsuitable choices. Vasodilator drugs, for example nitroprusside, nitroglycerin, phentolamine, and large doses of narcotics (which cause reduction of preload), should be used with caution. Considering that the murmur is best heard in the precordial area, the use of precordial stethoscope is strongly recommended. When an intraoperative arrhythmia appears in a patient who has documented mitral valve prolapse, the usual measures should be undertaken to establish the diagnosis and to rule out other causes before mitral valve malfunction is assumed to be the causative factor. If the arrhythmia is life-threatening, it should, however, be treated empirically without delay. If the arrhythmia is more benign (generally speaking atrial arrhythmias fall into this category), specific antiarrhythmic drugs can be employed. Unfortunately, the expected responses may not occur in patients with mitral valve prolapse. For example, a bradyarrhythmia may be resistant to atropine and require isoproterenol or artificial pacing. Premature ventricular contractions are often refractory to lidocaine, but frequently disappear spontaneously. If the arterial pressure is satisfactory, intravenous propranolol is the most effective drug for control of arrhythmias associated with mitral valve prolapse. The mechanism of action may simply be due to its nonspecific antiarrhythmic properties. Alternatively, it may increase left ventricular end diastolic volume, thus reducing the degree of valve prolapse.

Propranolol should be given intravenously in 0.5-mg doses while carefully monitoring the pulse rate and arterial pressure. In patients who do not have known mitral valve prolapse, there are certain clues that suggest the diagnosis. If during the preoperative physical examination the patient complains of a "whoop" murmur or palpitations, particularly in the case of a young woman with somewhat asthenic body habitus or a "straight" back, the condition should be suspected. Auscultation of the heart should be carefully performed in the left lateral decubitus position. If a murmur or click is heard, an echocardiogram is indicated. When faced with an arrhythmia appearing during surgery for no apparent reason, the usual measures should be adopted before presuming that mitral valve dysfunction is the culprit.

The principle of minimizing excessive cardiac emptying will have an important bearing on the selection of anesthetic technique. If general anesthesia is employed, it should be of sufficient depth to reduce the sympathetic response to surgical stimulation, remembering that undue peripheral vasodilatation is also undesirable. If narcotic supplementation of a nitrous oxide-oxygen relaxant technique is used, the same rule applies; namely, use of analgesics in amounts adequate to suppress reflex cardiovascular responses. If spinal or epidural anesthesia is considered appropriate, attention should be directed toward avoiding widespread vasodilation. Whenever possible, regional nerve block supplemented by adequate sedation is the anesthetic technique of choice, but epinephrine should not be added to the analgesic solution. Finally, the anesthesiologist must be aware of the hazards of operations performed in the sitting position in patients with mitral valve prolapse. There remains the intriguing question: could mitral valve prolapse have been responsible for many hitherto unexplained intraoperative arrhythmias? Certainly the frequency with which this abnormality is found suggests that this could well be the case.

## REFERENCES

1. Gallavardin L: Pseudo dedoublement du deusiene bruit de couer simulant le dedoublement mitral par bruit extracardique telesystolique swajoute. Lyon Med 121:409–413, 1913
2. Reid JVO: Mid-systolic click. S Afr Med J 35:353–355, 1961
3. Barlow JB, Pocock WA, Marchand P, et al: The significance of late systolic murmurs. Am Heart J 66:443–452, 1963
4. O'Rourke RA, Crawford MH, Johnson AD, et al: Prolapsed mitral valve leaflet syndrome. West J Med 122:217–231, 1975
5. Roberts WC, Pertloff JK: Mitral valvular disease: a clinicopathologic survey of the conditions causing the mitral valve to function abnormally. Ann Intern Med 77:939–975, 1972
6. Aranda JM, Befeler B, El-Sherif N, et al: Mitral valve prolapse: recent concepts and observations. Am J Med 60:997–1004, 1976
7. Chandranata P, Lopez JM, Fernandez JJ, et al: Echocardiographic evidence of tricuspid valve prolapse. Circulation 51: 823–826, 1975
8. Winkle RA, Lopes MG, Fitzgerald JW: Arrhythmias in patients with mitral valve prolapse. Circulation 52:73–81, 1975

9. Winkle RA, Lopes MC, Popp RL, et al: Life-threatening arrhythmias in the mitral valve prolapse syndrome. Am J Med 60:961-967, 1976
10. Koch FH, Hancock EW: Ten-year follow-up of 40 patients with the midsystolic click-late systolic murmur syndrome. Am J Cardiol 37:149, 1976
11. Leichtman D, Nelson R, Gobel FL, et al: Bradycardia with mitral valve prolapse. Ann Intern Med 85:453-457, 1976
12. Buda A, Levene DL, Myers MG, et al: Coronary artery spasm and mitral valve prolapse. Am Heart J 95:457-462, 1978
13. Imazaizumi T, Chandranata P, Wayne TF, et al: Transmural myocardial infarction with the prolapsed mitral leaflet syndrome and normal coronary arteries. Arch Intern Med 138:1354-1355, 1978

---

## Cough-Facilitated Conversion of Ventricular Tachycardia

Coughing has been shown to be helpful in altering the bradycardia and hypotension that may occur after intracoronary injections of contrast medium, and it can enable a patient to maintain consciousness during episodes of ventricular fibrillation and asystole. This report describes a patient with ischemic heart disease in whom 33 episodes of drug-refractory ventricular tachycardia were converted to normal sinus rhythm after abrupt forceful coughs were performed on command. When the patient was unable to cough as directed, external electric countershock was necessary to terminate the arrhythmia. These findings suggest that in isolated cases the cough may be effective in the conversion of potentially fatal ventricular tachyarrhythmias. (*Wei JY, Greene HL, Weisfeldt ML: Cough-facilitated conversion of ventricular tachycardia. Am J Cardiol 45:174-176, 1980*)

## Regionalization of Operations

This study examines mortality rates for 12 surgical procedures of varying complexity in 1498 hospitals to determine whether there is a relation between a hospital's surgical volume and its surgical mortality. The mortality of open-heart surgery, vascular surgery, transurethral resection of the prostate, and coronary bypass decreased with increasing number of operations. Hospitals in which 200 or more of these operations were done annually had death rates, adjusted for case mix, 25% to 41% lower than hospitals with lower volumes. For other procedures, the mortality curve flattened at lower volumes. For example, hospitals doing 50 to 100 total hip replacements attained a mortality rate for this procedure almost as low as that of hospitals doing 200 or more. Some procedures, such as cholecystectomy, showed no relation between volume and mortality. The results may reflect the effect of volume or experience on mortality, or referrals to institutions with better outcomes, as well as a number of other factors such as patient selection. Regardless of the explanation, these data support the value of regionalization for certain operations. (*Luft HS, Bunker JP, Enthoven AC: Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 301:1364-1369, 1979*)

ANESTH ANALG
59:384-385, 1980

# Herpangina in an Anesthesiologist

**Richard M. Rosenblatt, MD,* and George H. Domb, MD†**

A recent illness in a member of our anesthesia department prompted us to report this case which calls attention to the potential danger arising from a physician working while ill.

## Case Report

A previously healthy male anesthesiologist developed over a 24-hour period a 1-cm erythematous ulcer on the right anterior tonsillar pillar accompanied by a sore throat. Since systemic signs of infection were absent, the anesthesiologist continued to perform his normal duties in the operating room and in the obstetrical suite. The next day an ear, nose, and throat consultation was obtained because of malaise and increased discomfort with swallowing. Physical examination revealed only the intraoral lesion, cervical adenopathy, and no cutaneous lesions. The stomatitis, presumed by the anesthesiologist to be merely a herpetic lesion, was instead characteristic for herpangina. This infection is a contagious viral illness occurring primarily in children. Examination of the physician's 2-year-old child revealed a similar healing lesion in his oropharynx. Although herpangina is usually benign, in immunosuppressed or debilitated patients systemic disease can result and prove fatal. Accordingly, the physician ceased all clinical activities until the lesion resolved. Fortunately, no further cases ensued, and the physician returned to work the following week.

## Discussion

Herpangina is a contagious viral infection caused by Coxsackie virus groups A and B, and by some echoviruses.[1] While normally seen during summer epidemics in children, previously uninfected adults are susceptible. Infection is associated with a 4-day prodrome of malaise, odynophagia, cervical adenopathy, and transient fever followed by development of one or more vesicles on the soft palate or tonsillar area. The distinctive appearance of the initial vesicle is subsequently lost with repeated intra-oral abrasion. The mature lesion is an erythematous ulcer covered by a yellow fibrinous exudate and is indistinguishable from an aphthous ulcer ("canker sore"). In this case, the associated systemic symptoms and characteristic location of the lesion made the diagnosis of an aphthous ulcer unlikely. Other viral infections can also produce oral ulcerations, in particular, varicella ("chicken pox") and hand-foot-and-mouth disease. Varicella is easily diagnosed by the multitude of vesicles on the face and thorax. With hand-foot-and-mouth disease, 20 to 30 vesicles appear on the palms or soles concomitant with the oral lesions. Herpangina derives its name because occasionally chest pain is the predominant symptom.

No specific antiviral agent for herpangina is available, and isolation of carriers is crucial to prevent further spread. The contagious period of herpangina is short, lasting about 1 week and ending with resolution of the oral lesions. Although herpangina and most other Coxsackie infections generally evoke a mild benign illness, occasionally the disease can be more severe and even fatal: myocarditis, meningitis, hepatitis, and nephritis have been reported.[2] Transplacental spread of Coxsackie virus has been shown,[3, 4] and the fetus appears particularly susceptible since Coxsackie virus has been implicated as a cause of spontaneous abortion and congenital heart disease.[5, 6]

Herpangina is transmitted to susceptile individuals by contact with infected oral or respiratory secretions. The viral infection in this case was probably communicated from child to parent by direct personal contact. In most instances airborne transmission is the predominant mode of dissemination, particularly among adults. Airborne dissemination occurs because pathogens are entrapped in secretions that are expelled during expiration, sneezing, and coughing, forming an aerosol of small particles. A single sneeze produces nearly two million particles, 80% of which are less than 2.0 μ in diameter.[7(p6)] Such particles can remain airborne for prolonged periods. Knight[7(p2)] has calculated that a particle 10 μ in diameter requires almost 17 minutes to settle to the floor in a nonturbulent environment. Deposition of aerosolized virus within a recipient's respiratory tract is a function of the size of the particle. Particles ranging in size from 0.6 to 2.0 μ in diameter (before hygroscopic expansion) are retained predominantly in tertiary bronchi or alveolar ducts. Development of a clinical infection then depends upon the biologic properties of the virus and host: quantity of the inoculum, viability and virulence of the virus, susceptibility of the infected cells, and the host's immunity. Several studies have documented the transmission of Coxsackie viral infection by the airborne route. Gerone and Couch[8] detected viable airborne Coxsackie virus after infected patients sneezed and coughed. The same investigators sampled the air of rooms occupied by volunteers infected with Coxsackie A type 21 and recovered clinically significant quantities of live virus 2 to 4 hours after the rooms had been vacated. Finally, Couch et al[9] placed two groups of volunteers into a room divided by a filter designed to prevent direct passage of large droplets but not smaller airborne particles. One group was inoculated with Coxsackie virus; 50% of the second group, despite being on the opposite side of the partition, subsequently contracted the viral infection.

---

* Assistant Professor, Department of Anesthesiology.

† Resident, Department of Otorhinolaryngology.

Received from the Departments of Anesthesiology and Otorhinolaryngology, University of California, Davis-Sacramento Medical Center, Sacramento, California 95817. Accepted for publication January 2, 1980.

Reprint requests to Dr. Rosenblatt, Department of Anesthesiology, 4301 X Street.

As airborne particles are the primary mode for spread, wearing an operating room mask should reduce viral transmission; however, current masks are ineffective at filtering smaller-sized particles.[10-12] Thus a physician who harbors a Coxsackie infection and who continues to perform his operating room duties, albeit with a mask, is potentially a vector for viral dissemination.

The purpose in presenting this case is to illustrate the infectious disease hazards that exist for anesthesiologists and their patients. Despite recent concern regarding the occupational risks of anesthesiology, there have been no investigations into the prevalence of infectious diseases among anesthesiologists and the incidence of doctor-patient transmission. Substantive questions should be answered: (1) Are anesthesiologists a vector for transmitting infectious diseases to patients during the performance of their clinical duties? (2) How much in-hospital morbidity and mortality from infectious diseases is attributable to the practice of anesthesia? (3) Are anesthesiologists predisposed to contracting infectious diseases because of the nature of their work?

Without appropriate epidemiologic data, a scientific approach to infection control for anesthesiologists cannot be formulated. We do not think that physicians with nondebilitating infectious disease should continue to work. In the case presented the potential for widespread dissemination existed. Only professional diligence by the individual physician prevented such an occurrence since there are no work abstinence guidelines. Certainly an infection control policy is warranted given the prevalence of herpangina and other viral diseases.

## REFERENCES

1. Chole RA, Domb GH: Differential diagnosis of superficial ulcerations of the oral mucosa. Otolaryngology and Head and Neck Surgery, 87:734–740, 1979
2. Lerner M: Euteric viruses, in Harrison's Principles of Internal Medicine. Edited by M Wintrobe. New York, McGraw-Hill Co, 1970, pp 963
3. Grist NR, Bell EJ: Coxsackie viruses and the heart. Am Heart J 77:295–300, 1969
4. Selzer G: Transplacental infection of the mouse fetus by Coxsackie viruses. Isr J Med Sci 4:125, 1969
5. Brown GC, Evans TN: Serologic evidence of Coxsackie-virus etiology of congenital heart disease. JAMA 199:183–187, 1967
6. Czeizel A: Coxsackie virus and congenital malformation. JAMA 201:142, 1967
7. Knight V: Viral and Myocoplasmal Infections of the Respiratory Tract. First edition. London, Henry Kimpton Publishers, 1973, pp 2, 6
8. Gerone PJ, Couch RB, Keefer GV, et al: Assessment of experimental and natural viral aerosols. Bacteriol Rev 30:576, 1966
9. Couch RG, Douglas RB, Lindgren KM, et al: Airborne transmission of respiratory infection with Coxsackie virus A type 21. Am J Epidemiol 91:78–86, 1970
10. Ritter MA, Eitzen H, French ML, et al: The operating room environment as affected by people and the surgical face mask. Clin Orthop 111:147–150, 1975
11. Quesnel LB: The efficiency of surgical masks of varying design and composition. Br J Surg 62:936–940, 1975
12. Ginsberg F: Stop masking the facts: studies show gauze masks are not effective in OR. Mod Hosp 114:132, 1970

ANESTH ANALG
59:386–387, 1980

# Acute Myocardial Ischemia Caused by Mediastinal Chest Tube Suction

**James W. Chapin, MD,* James Kahre, MD,† and Myrna Newland, MD***

Acute myocardial ischemia following successful weaning from cardiopulmonary bypass occurred in two patients who underwent correction of atrial septal defects. In both cases the ischemia episode was detected by ECG changes. The most likely cause in both was suction applied to mediastinal chest tubes interfering with myocardial perfusion. This complication of chest tubes has not been previously reported.

## Case Reports

### Case 1

A 6½-year-old male child with left to right shunt through a secundum atrial septal defect (ASD) underwent surgical correction. There was no impairment of activity due to the cardiac defect and the remainder of the history and physical examination was negative. A halothane-$N_2O/O_2$ anesthetic was used. The ASD was closed during normothermic cardiopulmonary bypass without incident. Weaning from bypass was unremarkable and serum electrolyte levels and arterial blood gas tensions were within normal limits except for a low ionized calcium level. Incremental doses of calcium chloride (400 mg total) were administered over a 90-minute period.

An hour after discontinuation of cardiopulmonary bypass two Argyle #28 French thoracic catheters were placed, one inside the pericardium and the other outside the pericardium. The pericardium was closed with interrupted 4-0 black silk and the pericardial tube was attached to wall suction (450 mm Hg) while the Pleur-evac was being assembled. The sternum was still open. Within minutes after suction was applied an acute 7.5-mm elevation of the ST segment of lead II ECG pattern was noted by the anesthesiologist. Arterial and atrial pressures remained stable and the heart rate dropped from 130 to 100 beats per minute. Nitrous oxide was discontinued, 100% $O_2$ was administered, and the halothane concentration was decreased from 1% to 0.5%. Recent blood gas tensions and serum electrolyte levels were normal. The only possible related event was application of suction to the mediastinal chest tube. The suction was discontinued and within a minute the injury pattern on the ECG reverted to a normal pattern. There were no sequelae from this incident.

### Case 2

A 2-year-old, 11-kg female infant underwent surgical correction of an ASD about 3 months after case 1. This patient was also asymptomatic and had no other health problems.

The child was premedicated with meperidine (25 mg) and atropine (0.1 mg) intramuscularly. A halothane-$N_2O/O_2$ anesthetic technique was used. The surgical repair and weaning from cardiopulmonary bypass went without incident. One Argyle #20 French thoracic catheter was placed in the right chest and a second was placed inside the pericardium. The pericardium was then closed and the pericardial tube connected to a Pleur-evac with 20 cm $H_2O$ negative pressure. Within a few minutes lead II of the ECG changed from a normal sinus rhythm to tachycardia-bradycardia with an acute injury pattern. Because of the similar incident in case 1 3 months earlier, the suction was discontinued and the ECG pattern reverted to normal within a minute. No sequelae have been observed in this child.

## Discussion

The temporal relationship strongly suggests that the suction applied to a mediastinal tube interfered with adequate myocardial oxygenation in these two cases. Possible mechanisms include coronary artery obstruction or compression of the myocardial wall by suction. This is apparently the first report of this type of mechanical interference of coronary flow.

Other mechanical causes of inadequate coronary flow at the conclusion of open-heart surgery include occlusion by suture,[1] edema, clot, or air. These probably would have caused problems earlier in the period following the bypass rather than later, as in the cases just reported. In addition, myocardial ischemia can occur secondary to inadequate preservation of the myocardium during cardiopulmonary bypass as recently discussed by Kirklin et al.[2] This, too, would

---

* Assistant Professor.

† Resident in Anesthesia.

Received from the Department of Anesthesiology, University of Nebraska Medical Center, 42nd Street and Dewey Avenues, Omaha, Nebraska 68105. Accepted for publication January 8, 1979.

Reprint requests to Dr. Chapin.

have been evident earlier in the period following the bypass and would not have been reversed by discontinuing suction of the mediastinal tube.

Anesthesiologists should be aware that suction applied to mediastinal chest tubes can produce sudden and severe myocardial ischemia.

### REFERENCES

1. Anderson KR, McGoon DC, Lie JT: Vulnerability of coronary arteries in surgery for transposition of the great arteries. J Thorac Cardiovasc Surg 76:135–139, 1978
2. Kirklin JW, Conti VR, Blackstone EH: Prevention of myocardial damage during cardiac operations. N Engl J Med 301:135–141, 1979

---

## Stopping Smoking Increases Oxygen Availability

The effects of stopping smoking for 48 hours on factors governing the availability of oxgyen from the blood (carboxyhemoglobin (COHb), hemoglobin-oxygen ($HbO_2$) affinity, and hemoglobin concentration) were measured in the last trimester of pregnancy. Three groups were studied: smokers, smokers who stopped smoking for 48 hours, and nonsmokers. The 22 smokers had higher initial COHb values and greater $HbO_2$ affinity than the 10 nonsmokers, but their total hemoglobin concentrations were also higher, so that their oxygen availability was not significantly reduced. In the 11 smokers who stopped, the reduction of COHb and decrease in $HbO_2$ affinity led to a significant 8% increase in available oxygen in 48 hours. Since even small improvements in oxygen delivery to the tissues may confer critical benefit to the fetus, particularly during labor when there is exposure to general anesthesia, the authors suggest that smoking should be discouraged for 48 hours before elective deliveries. (*Davies JM, Latto IP, Jones JG, et al: Effects of stopping smoking for 48 hours on oxygen availability from the blood: A study on pregnant women. Br Med J 2:355–356, 1979*)

## Indications for Admission to a Coronary Care Unit

One hundred cases with an admission diagnosis of acute coronary insufficiency or unstable angina were reviewed to establish criteria for admission to a coronary care unit. Myocardial infarction was subsequently diagnosed in 20 of the patients. Ventricular tachycardia occurred in 16 patients and ventricular fibrillation in one patient. Clinical features found to predict an increased risk of myocardial infarction included chest pain for more than 30 minutes within 24 hours prior to admission, new nonspecific electrocardiographic abnormalities consistent with ischemia, and diaphoresis. All patients with ventricular tachyarrhythmias had presented with both prolonged chest pain prior to admission and new electrocardiographic changes. The sensitivity, specificity, and predictive value of various clinical criteria for identifying patients likely to have a myocardial infarction were calculated, and criteria with very high (greater than 90%) sensitivity were identified. These could be used to establish which patients are at increased risk of myocardial infarction and therefore require admission to a coronary care unit. (*Nattel S, Warnica JW, Ogilvie RI: Indications for admission to a coronary care unit in patients with unstable angina. Can Med Assoc J 122:180–184, 1980*)

ANESTH ANALG
59:388-390, 1980

# Chemodectoma Diagnosed by Hypertension and Tachycardia during Anesthesia

**Myrna C. Newland, MD,* and Barbara J. Hurlbert, MD***

In children, tumors of the neck may include lymphoma, neuroblastoma, endothelioma, branchial cleft cyst, thyroid tumor, and others more unusual such as chemodectoma, i.e., paraganglioma of the carotid body. More than 500 cases of nonfunctional carotid body paragangliomas have been reported. We have found reports[1-4] of four cases of functionally active carotid body tumors.

We present a case of functionally active carotid body chemodectoma to acquaint anesthesiologists with this rare tumor so that they may include it in their differential diagnosis in considering the management of anesthesia for patients with neck masses.

## Case Report

A 13-year-old white female adolescent was referred to this hospital for evaluation of a heart murmur, multiple joint pains and swelling, occasional low grade fevers, and weight loss of 4.5 kg.

On admission she weighed 27.4 kg; temperature was 36.9 C, respirations 24 per minute, and blood pressure 98/50 torr. Her heart rate was 136 beats per minute initially but subsequently was 86 to 100 beats per minute throughout the preoperative period. Small bilateral nodes were palpable in the neck and a 2.5x8-cm firm mass was present just below the angle of the jaw on the left side. A grade IV/VI systolic ejection murmur was noted over the precordium which was not transmitted to the back or neck. Her right wrist was warm, tender, with moderate swelling and pain on movement.

Laboratory data included a sedimentation rate of 44 mm/hr, an ASO titer less than 100, and a white blood count of 16,900/mm$^3$ with a left shift. ECG showed prolongation of the PR interval. Chest roentgenogram was consistent with dilation of the ascending aorta. An echocardiogram was suggestive of a subaortic ridge with vegetative lesions. The impression was bacterial endocarditis for which she was treated with intravenous oxacillin and gentamicin. Blood cultures failed to confirm the diagnosis of bacterial endocarditis.

In an effort to make a definitive diagnosis, the patient was scheduled for biopsy of the mass in her left neck. At the preanesthetic visit she was anxious and diaphoretic but afebrile. Vital signs and a physical examination revealed no changes. In the preoperative room heart rate was 136 beats per minute and systolic blood pressure 160 torr. These values remained unchanged after 60 mg of meperidine was given slowly intravenously.

Anesthesia was induced with thiopental, 150 mg IV, and 60% $N_2O$/40% $O_2$ by face mask was begun. A sinus tachycardia of 190 beats per minute suddenly developed. Blood pressure, difficult to obtain by auscultation or palpation, was 160 torr systolic by Doppler ultrasound flow probe. An additional 250 mg of thiopental was given with no change in the heart rate or blood pressure. Rectal temperature remained 37 C. Venous and arterial blood gas tensions were within normal limits.

Ventilation was maintained by mask with 100% oxygen. Propranolol, 1 mg, was given slowly intravenously. This decreased the heart rate to 130 beats per minute and blood pressure to 100/70 torr. The operation was postponed. Due to her response under anesthesia, a catecholamine-secreting tumor was suspected. A subsequent measurement of urine showed a vanillylmandelic acid (VMA) level of 34.9 mg/24 hr (10 times normal). Venous plasma catecholamine level was 3,714 ng/100 ml (more than 100 times normal). After the diagnosis of a catecholamine-secreting tumor was made, a continuous infusion of phentolamine was started and maintained thereafter at 2.5 mg/hr up to and including induction of anesthesia for resection of the tumor 48 hours later.

On arrival in the preoperative room she was apprehensive, markedly diaphoretic, and peripherally vasoconstricted. Blood pressure was 160/120 torr and heart rate 130 beats per minute. She was premedicated with meperidine (30 mg) and droperidol (5 mg) intravenously. After ECG, chest stethoscope, blood pressure cuff, and a Doppler flow probe were placed, anesthesia was induced with incremental doses of intravenous thiopental (up to 500 mg) in 30 minutes while 2% enflurane was administered. Two intravenous infusions were begun and an arterial line was established. Following 30 minutes of 2% enflurane the trachea was intubated with the aid of succinylcholine (30 mg IV) without change in vital signs. The operation proceeded for 1 hour and 15 minutes with blood pressure between 120 to 140 torr systolic and heart rate at 120 beats per minute until extensive manipulation of the tumor was required to remove it. At this time blood pressure increased to 180/100 torr and

---

* Assistant Professor.

Received from the Department of Anesthesiology, University of Nebraska Medical Center, Omaha, Nebraska 68105. Accepted for publication January 10, 1979.

Reprint requests to Dr. Newland.

heart rate to 140 beats per minute. The phentolamine was increased to 8 mg/hr to control the patient's blood pressure at 140/100 torr during excision of the tumor. As was expected, when the veins draining the tumor were ligated, blood pressure decreased from 150/100 torr to 70/50 torr in less than 5 minutes in spite of the phentolamine being discontinued prior to ligation of the veins. Transfusion of 500 ml of whole blood was begun in anticipation of the expected vasodilation with lack of catecholamine stimulation. She required 1000 ml of whole blood for an estimated 550-ml blood loss to maintain her pressure at 120/70 torr. Following excision of the tumor vital signs remained stable throughout the remainder of surgery and into the recovery period without the use of vasoactive drugs.

Recovery was uneventful. Pathologic diagnosis was carotid body paraganglioma (chemodectoma). Postoperatively she underwent a combined course of chemotherapy and radiotherapy because at operation the mass was found to extend into the calvarium along the internal jugular vein and could not be totally excised. She is asymptomatic and has normal blood catecholamine levels at this time.

## Discussion

Paraganglia consisting of cell groups associated with the autonomic nervous system are distributed throughout the body. Carotid paraganglia (carotid bodies) function as chemoreceptors for regulation of respiration. All paraganglia, including the chemoreceptors, store catecholamines in granules. Functional catecholamine-secreting neoplasms may originate in any paraganglia. The morphology, location and function of these tumors have been reviewed by Glenner and Grimley.[5] The vast majority of carotid body paraganglia tumors are benign and nonfunctional; all of the 90 reported cases studied by Shamblin et al[6] at the Mayo Clinic were functionally inactive.

Most reported cases of carotid body paraganglia tumors have been seen as painless neck masses and have been biopsied or excised uneventfully. We are aware of only four reported cases of functional catecholamine-secreting carotid body tumors, the first of which was reported in 1962 by Glenner et al.[1] Of these four cases, three were seen preoperatively with symptoms suggestive of episodic catecholamine release.[1,3,4] The fourth patient, although asymptomatic preoperatively, had increased urinary levels of norepinephrine indicating increased catecholamine production.[2] Two of the four patients died, one intraoperatively[1] and the other postoperatively with cerebral infarction.[3] Prior to induction of anesthesia for her first procedure, our patient did not have symptoms of a catecholamine-secreting tumor such as hypertension and tachycardia, although she had a nonspecific weight loss and anxiety and one isolated instance of tachycardia on admission which was attributed to anxiety and possible sepsis. Following this single episode of tachycardia her heart rate was 85 to 100 beats per minute. A catecholamine-secreting tumor had not been considered with her symptom complex of fever, neck mass, heart murmur, and single joint pain prior to her first anésthetic for excisional biopsy of the neck mass.

A diagnosis of a catecholamine-secreting tumor was considered following her initial anesthetic. Careful questioning of her mother at that time revealed frequent night sweats requiring one or two changes of bed clothes per night occurring periodically for 1 year, information which had not been elicited on previous questioning. The neck mass was noted on a preschool physical examination 1 year prior to this admission.

We present this example of a patient with an apparently benign history in whom the signs of excessive catecholamine release were apparent only after general anesthesia was induced.

The chemical activity of the functional paragangliomas is essentially no different from that of a pheochromocytoma.[7] Anesthetic management of a secreting chemodectoma is physiologically and pharmacologically the same as management of a pheochromocytoma. Intraoperative problems include a contracted blood volume, hypertension, tachycardia, dysrhythmias and rapid swings in blood pressure. Preoperative administration of alpha-blockers such as phentolamine[8] or dibenzyline[9] is recommended, though it is often unnecessary or even impossible to restore blood pressures to normal levels preoperatively with these agents. The chief value of these drugs is to restore blood volume, thus avoiding intraoperative fluctuations in blood pressures.[8] Preoperative and intraoperative use of propranolol for beta adrenergic blockade has also been advocated to prevent tachycardia and dysrhythmias during anesthesia and surgery.[10] Our patient was prepared preoperatively with a phentolamine infusion plus fluid and albumin administration to restore blood volume. The phentolamine infusion was regulated intraoperatively to maintain systolic blood pressure between 120 to 140 torr with the manipulation of the tumor. Propranolol was available, if needed, for extreme tachycardia or dysrhythmias. Her heart rate remained between 120 to 140 beats per minute throughout this procedure without propranolol.

Induction of anesthesia and endotracheal intubation are potentially hazardous events in the lightly anesthetized patient with catecholamine-secreting tumor. Adequate depth of anesthesia should be achieved prior to intubation.[11] Our patient was adequately anesthetized during the second anesthetic following 30 minutes of 2% enflurane prior to tracheal intubation as demonstrated by the absence of changes in vital signs following intubation.

Although many anesthetic agents and techniques have been used, enflurane has been advocated most recently in catecholamine-secreting tumors because of lack of myocardial sensitization.[12,13] Because of these reports we chose to use enflurane. Despite stopping the phentolamine infusion and despite volume expansion with whole blood, this patient's blood pressure decreased upon ligation of the venous drainage of the tumor. Hypotension is most common at this time.[8] With volume expansion the hypotension resolved and vasoactive drugs were not required.

The pain and swelling of her right wrist, which was unrelated to her chemodectoma, subsided during hospitalization. On follow-up examination she has had no recurrence of joint pain or swelling. Since arthritis is not associated with chemodectoma, this symptom complex remains unexplained.

In summary, although very rare, the possibility of a catecholamine-secreting paraganglioma (chemodectoma) should be considered in patients with neck masses. In our patient the heart murmur, weight loss, and anxiety were not correlated to a secreting tumor in the neck preoperatively and were only explained once tachycardia and paroxysmal hypertension occurred during anesthesia. Once the diagnosis of chemodectoma is apparent, anesthetic management is similar to that for a pheochromocytoma.

## REFERENCES

1. Glenner GG, Crout JR, Roberts WC: A functional carotid-body-like tumor. Arch Pathol. 73:66–76, 1962
2. Berdal P, Bratten M, Cappelin C, et al: Noradrenaline-adrenaline producing nonchromaffin paraganglioma. Acta Med Scand 172:249–257, 1962
3. Hamberger CA, Hamberger CB, Wersall J, et al: Malignant catecholamine-producing tumor of the carotid body. Acta Pathol Microbiol Scand 69:489–492, 1967
4. Clarke AD, Matheson H, Boddie HG: Removal of catecholamine-secreting chemodectoma. Anaesthesia 31:1225–1230, 1976
5. Glenner GG, Grimley PM: Tumors of the extra-adrenal paraganglion system (including chemoreceptors), in Atlas of Tumor Pathology, Second Series, Fascicle 9. Washington, DC, Armed Forces Institute of Pathology, 1974
6. Shamblin WR, ReMine WH, Sheps SG, et al: Carotid body tumor (chemodectoma): clinicopathologic analysis of ninety cases. Am J Surg 122:732–739, 1971
7. Levit SA, Sheps SG, Espinosa RE, et al: Catecholamine-secreting paraganglioma of glomus jugulare region resembling pheochromocytoma N Engl J Med 281:805–811, 1969
8. Goldfein A: Pheochromocytoma: diagnosis and anesthetic and surgical management. Anesthesiology 24:462–471, 1963
9. Ross EJ, Edwards D, Robertson AI, et al: The management of cases of pheochromocytoma. Proc R Soc Med 55:427–436, 1962
10. Cooperman LH, Engelman K, Mann PEG: Anesthetic management of pheochromocytoma employing halothane and beta adrenergic blockade. Anesthesiology 28:575–582, 1967
11. Gebbie DM, Finlayson DC: Use of alpha and beta adrenergic blocking drugs and halothane in the anaesthetic management of phaeochromocytoma. Can Anaesth Soc J 14:39–43, 1967
12. Kreul JF, Dauchot PJ, Anton AH: Hemodynamic and catecholamine studies during pheochromocytoma resection under Ēthrane anesthesia. Anesthesiology 44:265–268, 1976
13. Janeczko GF, Ivanovich AD, Glisson SN, et al: Enflurane anesthesia for surgical removal of pheochromocytoma. Anesth Analg 56:62–67, 1977

ANESTH ANALG
59:391-392, 1980

# Anesthetic Considerations in Pregnant Patients Receiving Terbutaline Therapy

**R. Ravindran, MD,* O. J. Viegas, MD,***
**L. M. Padilla, MD,* and**
**P. LaBlonde, MD†**

Terbutaline, a selective $\beta_2$ adrenergic agonist,[1] is primarily used for the treatment of bronchial asthma. Although the Food and Drug Administration has not approved its use for relaxation of the uterus, terbutaline is, with the consent of the patient, increasingly administered to prevent premature labor following cervical cerclage, to arrest premature labor in the 24th to 32nd weeks of pregnancy,[2] to improve uteroplacental blood flow in the presence of fetal distress,[3] to relax hypertonic uterus, and to stop labor in patients with genital herpes. Side effects when so used include palpitations, tremor, slight increase in systolic blood pressure, slight decrease in diastolic pressure,[4] hyperglycemia, and occasional pulmonary edema. No adverse fetal effects have been reported.[5] We have administered regional or general anesthesia to 25 patients who were receiving terbutaline. Three of these patients developed significant complications during anesthesia. Prior to the administration of terbutaline these patients had normal blood chemistries, chest x-rays, and ECGs.

## Case Reports

### Case 1

A 24-year-old gravida 3 para 0 woman weighing 70 kg was admitted to the hospital at 24 weeks of gestation for surgical correction of cervical incompetence. She had a previously diagnosed but asymptomatic atrial septal defect. Physical examination was normal except for the presence of a systolic murmur. Blood pressure was 100/70 torr, heart rate 90 beats per minute, and respiratory rate 18/min. The consulting cardiologist agreed to the proposed administration of terbutaline. Anesthesia was induced with thiopental (275 mg) and tracheal intubation was facilitated with the administration of succinylcholine (80 mg IV). Following tracheal intubation, normal breath sounds were heard bilaterally. Anesthesia was maintained with fentanyl and nitrous oxide-oxygen. Immediately prior to the commencement of surgery and 15 minutes following induction of anesthesia, 0.25 mg of terbutaline was given intravenously. Immediately following injection of terbutaline the patient's heart rate increased to 140 beats per minute but then decreased to 110 to 120 beats per minute within 5 minutes and remained at that rate until the conclusion of surgery. Systolic blood pressure ranged from 100 to 110 torr. Cardiac dysrhythmias were not observed on the monitor. During the operation she received 300 ml of lactated Ringer's solution. In the recovery room the patient complained of difficulty in breathing. Examination of the chest revealed bilateral basilar rales. Neuromuscular function was normal. The head of the bed was elevated and oxygen was administered by mask. A portable chest x-ray revealed bilateral pulmonary edema. She improved in 1 hour following administration of furosemide (20 mg IV). Chest x-ray taken 2 hours following administration of furosemide was normal.

### Case 2

A 23-year-old gravida 4 para 3 woman weighing 75 kg was admitted to the hospital for labor and delivery. Because of 24-hour history of ruptured membranes and increased possibility of development of chorioamnionitis labor was augmented with oxytocin infusion of 5 to 20 μg/min IV. After 5 hours of stimulation three episodes of variable decelerations were noted. The fetal scalp blood pH was 7.13. The patient was taken to surgery for emergency cesarean section. Preoperatively her heart rate was 110 beats per minute and blood pressure 110/70 torr. Since she was having active uterine contractions 0.25 mg of terbutaline was given intravenously to relax the uterus and to improve uteroplacental circulation. Following injection of terbutaline her heart rate increased to 130 beats per minute but the blood pressure remained 110/70 torr. Anesthesia was induced with thiopental (275 mg) and endotracheal intubation performed after administration of succinylcholine (80 mg IV). During induction and intubation the patient's heart rate increased to 180 beats per minute and the blood pressure dropped to 80/60 torr. Other than the sinus tachycardia no cardiac dysrhythmias were observed. Carotid massage was ineffective in decreasing the heart rate. Edrophonium (2.5 mg) given intravenously reduced the heart rate to 80 beats per minute and increased the blood pressure to 110/70 torr. Anesthesia was continued with nitrous oxide-oxygen and fentanyl following the delivery of the infant. The maternal heart rate ranged from 120 to 130 beats per minute and the systolic blood pressure from 110 to 130 torr throughout the remainder of surgery. The infant had Apgar scores of 6 and

---

* Assistant Professor.

† Resident.

Received from the Department of Anesthesiology, Indiana University Medical Center, 1000 West 10th Street, Indianapolis, Indiana 46202. Accepted for publication January 12, 1980.

Reprint requests to Dr. Ravindran.

8 at 1 and 5 minutes, respectively. The maternal heart rate decreased to preoperative levels within 1 hour after completion of surgery.

### Case 3

A 26-year-old gravida 3 para 0 woman weighing 72 kg in the 26th week of pregnancy was admitted to the hospital with abdominal cramps. Pelvic examination revealed the cervix to be 4 cm dilated and the membranes bulging. She was given morphine (10 mg) and terbutaline (0.25 mg IV). Following the terbutaline her uterine cramping subsided. On the following day, 18 hours after intravenous administration of terbutaline, she was taken to the operating room for cervical cerclage. Anesthesia was induced with thiopental (275 mg) and endotracheal intubation facilitated with administration of succinylcholine (80 mg IV). Anesthesia was maintained with 1% to 1.5% halothane and 60/40 nitrous oxide and oxygen. Fifteen minutes after induction of anesthesia, and just prior to the commencement of surgery, 0.25 mg of terbutaline was given intravenously to prevent premature contraction of the uterus. Immediately the heart rate increased from 90 to 130 beats per minute. Three episodes of ventricular bigeminy followed by multifocal premature ventricular contractions occurred. Hyperventilation did not restore normal rhythm. Lidocaine (75 mg) was administered intravenously and halothane was discontinued. The remainder of the operation was completed with fentanyl, nitrous oxide, and oxygen without recurrence of ventricular dysrhythmias.

## Discussion

Terbutaline, a selective $\beta_2$ adrenergic agonist, is approved for use only in the treatment of bronchial asthma. The FDA has not approved its use for the relaxation of the uterus or for intravenous use. However, because of its effectiveness in relaxing the uterus terbutaline is, with the consent of the patient, widely used in many teaching institutions and in some community hospitals to stop labor. As a result, anesthesiologists may be presented with patients given terbutaline prior to cervical cerclage, cesarean section, or with premature labor. Though it is considered to be a selective $\beta_2$ agonist, terbutaline appears also to have moderate $\beta_1$ receptor activity as evidenced by a moderate positive chronotropic effect.[1,6] In case 1, the rapid ventricular response in a previously asymptomatic heart patient probably caused pulmonary edema. Pulmonary edema has also been reported in a noncardiac patient with the simultaneous administration of terbutaline and dexamethasone.[7] In our institution we have observed the development of pulmonary edema in three unanesthetized pregnant patients at various times following the intravenous administration of terbutaline. The etiology of pulmonary edema occurring in pregnant patients given terbulaine is not known. Perhaps pregnant patients who have increased cardiac output and increased blood volume do not tolerate a rapid increase in heart rate. In case 2 terbutaline enhanced the chronotropic response one normally sees on laryngscopy and intubation. This rapid increase in heart rate might have contributed to the reduction in blood pressure. Following a bolus intravenous administration of terbutaline usually the heart rate increases and the blood pressure decreases. These changes are maximal within 5 minutes and gradually return to the control levels within 2 hours.[6] In case 3 we believe terbutaline probably contributed to the development of dysrhythmias. Dysrhythmias have been reported to occur with the use of beta-adrenergic agonists such as epinephrine when administered to patients anesthetized with halothane. We are not aware of studies indicating the safe limits of administration of terbutaline in patients anesthetized with halothane.

Based on our experience, we feel that terbutaline should be administered as an intravenous bolus at least 10 minutes prior to induction of anesthesia to prevent its peak cardiovascular effect from occurring during induction and intubation. Halothane, because of its myocardial depression effect and sensitization of myocardium to the effects of beta agonists, should be avoided in patients receiving terbutaline. Because of increased possibility of cardiac decompensation occurring in pregnant patients receiving terbutaline intraoperative fluid administration needs to be closely monitored. Furthermore, terbutaline should be avoided in patients with cardiac disease or preeclampsia as it might induce significant hemodynamic alterations.

### REFERENCES

1. Persson H, Olsson T: Some pharmacological properties of terbutaline (INN), 1-(3,5-dihydroxyphenyl)-2-(t-butylamino)-ethanol: a new sympathomimetic $\beta$ receptor-stimulating agent. Acta Med Scand 512 (Suppl): 11–18, 1970
2. Andersson KE, Bengtsson LPH, Gustafson I: The relaxing effect of terbutaline on the human uterus during labor. Am J Obstet Gynecol 121:602–609, 1975
3. Arias F: Intrauterine resuscitation with terbutaline: a method for the management of acute intrapartum fetal distress. Am J Obstet Gynecol 131:39–43, 1978
4. Lawyer C: Problems with terbutaline. N Engl J Med 296:821–822, 1977
5. Ingemarsson I: Effect of terbutaline on premature labor. Am J Obstet Gynecol 125:520–524, 1976
6. Caritis SN, Mueller-Heubach E, Norishima HO, et al: Effect of terbutaline on cardiovascular state and uterine blood flow in pregnant ewes. Obstet Gynecol 50:603–606, 1977
7. Stubblefield PG: Pulmonary edema occurring after therapy with dexamethasone and terbutaline for premature labor. Am J Obstet Gynecol 132:341–342, 1978

# letters
# TO THE EDITOR

## Pancuronium and Gentamicin Interaction in Patients with Renal Failure

To the Editor:

Recent experience at University Hospitals of Cleveland indicates that there may be reason for concern in renal transplant patients who receive pancuronium bromide (Pavulon) in combination with injectable gentamicin sulfate (Garamicin).

Renal transplantation is a fairly common procedure at our institution. In recent years many such patients have received pancuronium bromide for endotracheal intubation and intraoperative relaxation. None was known to have experienced an unusual reaction. In the past year, however, four renal transplant patients have required dialysis to regain full muscle strength following surgery.

Since several surgeons perform renal transplants at our institution, the use of antibiotics and other drugs varies. The four cases mentioned above occurred with one surgeon who uses large doses of gentamicin sulfate and mannitol.

Although 0.5 mg/kg of gentamicin, or steroids, or both seemed not to affect other patients of ours, respiratory failure occurred in four patients who received gentamicin sulfate, 1.5 mg/kg IV, preoperatively and intraoperatively. The four patients were black men who had recently undergone dialysis; they were in relatively good physical condition. They all received mannitol, or steroids, or both.

The first three patients underwent dialysis the next day after ruling out electrolyte, glucose, and other metabolic disturbances. The first patient even had a lumbar puncture and CT scan. All patients regained consciousness during dialysis and pulled out their endotracheal tubes. All three patients continued to do well and were discharged.

The fourth patient underwent dialysis later on the day of operation to avoid continued artificial respiration. He immediately responded in the same manner as above.

Subsequent patients have been given curare instead of pancuronium; steroids, mannitol, and 1.5 mg/kg of gentamicin also have been given. There were no problems with respiratory failure.

Several drug interactions may have been involved in these four cases. It is now known that the breakdown products of pancuronium bromide can, with impaired excretion, cause a neuromuscular blockade. The "mycins" also do this and mannitol[1] can enhance this blockade. Another possibility is the anesthetic effect of pancuronium. Does pancuronium have a central depressive effect similar to the previously used steroid anesthetic hydroxydione sodium hemisuccinate (Viadril)? It has recently been shown that MAC is decreased and clinically anesthesia requirements are notably decreased by pancuronium.[2]

Audrey G. Regan, MD
*Assistant Professor*
Prasad P. V. Perumbetti, MD
*Resident*
*Department of Anesthesia*
*Case Western Reserve University*
*School of Medicine*
*Cleveland, Ohio 44106*

REFERENCES

1. Miller RD, Sohn YJ, Matteo RS: Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. Anesthesiology 45:442–445, 1976
2. Forbes AR, Cohen NH, Eger EI II: Pancuronium reduces halothane requirement in man. Anesth Analg 58:497–499, 1979

---

## Failure of a Cephalothin Test Dose to Produce Anaphylaxis

To the Editor:

Two articles documenting anaphylactic reactions to cephalothin have appeared in the anesthesia literature.[1, 2] We recently encountered a case which is different from those previously documented in that an intravenous test dose of cephalothin failed to produce anaphylaxis, but a subsequent larger bolus resulted in classic anaphylactic shock.

Our patient was scheduled for elective bone graft and internal fixation of the left tibia and fibula. Subarachnoid block with an anesthetic level of T-8 was performed uneventfully. Because of a prior urticarial reaction to penicillin, a 140-mg test dose of cephalothin was administered intravenously. No untoward reactions or alterations in vital signs were noted. Seven minutes later, the remainder of the 1-g dose was given intravenously followed within 2 minutes by the clinical signs and symptoms of anaphylactic shock including unobtainable blood pressure and pulse, bradycardia, diminished respiratory excursions and wheezing, cyanosis, generalized edema, erythema, and urticaria. The patient was resuscitated with controlled respiration by mask with 100% oxygen and the administration of intravenous fluids, diphenhydramine, hydrocortisone, and ephedrine sulfate. Surgery was postponed. The patient recovered fully and underwent uneventful surgery and general anesthesia 5 days later.

Although anaphylactic reaction may occur up to 1 hour after exposure to antigen,[3] the usual onset after a relatively large bolus, especially when administered intravenously, is within a few minutes. The failure to develop anaphylaxis within a 7-minute period is unusual and may represent either a false-negative response or a delayed positive response to the antigen test dose. Which mechanism was responsible is unclear, but our case indicates that potentially fatal anaphylaxis cannot be predicted. Skin testing may not be reliable and a test dose may cause an anaphylactic reaction in itself or a negative result as in our patient, which may not exclude a subsequent reaction. Prompt diagnosis and initiation of therapy are essential to prevent death.

Suzanne S. Zeok, MD
*Assistant Clinical Professor*
Kentaro Tsueda, MD
*Associate Professor and Clinical Director*
*Department of Anesthesiology*
*University of Kentucky*
*Albert B. Chandler Medical Center*
*Lexington, Kentucky 40506*

REFERENCES

1. Velazquez JL, Gold MI: Anaphylactic reaction to cephalothin during spinal anesthesia. Anesthesiology 43:476–478, 1975
2. Barnett AS, Hirshman CA: Anaphylactic reaction to cephaprin during spinal anesthesia. Anesth Analg 58:337–338, 1979
3. MacFarlane M, McCarron M: Anaphylactic shock and anaphylactoid reaction. Drug Intell Clin Pharm 7:394–407, 1973

# Anticoagulants and Continuous Epidural Anesthesia

To the Editor:

A recent study[1] by Lunn, Dannemiller, and Stanley involved continuous epidural anesthesia for aortic reconstructive surgery. Presumably the patients were given heparin intraoperatively. Spinal epidural hematomas have been reported in patients who had lumbar punctures performed followed by administration of anticoagulants.[2-6] The same complication might occur after placement of catheters in the epidural space when heparin is subsequently administered. The authors make no mention of this potential complication. Was the technique for placement of the catheter modified in any way? Was continuous epidural anesthesia abandoned or surgery delayed in the case of a traumatic tap, or was the dose of heparin modified? What was the time interval between placement of the epidural catheter and heparinization? What monitoring was undertaken to provide early diagnosis of a spinal epidural hematoma in the event one were to occur?

Finally, were any complications other than cardiovascular instability encountered in the study group or in other patients who have undergone aortic replacement under epidural anesthesia at the authors' institution?

James D. McCullough, MD
*Department of Anesthesiology*
*University of Michigan Medical Center*
*Ann Arbor, Michigan 48109*

REFERENCES

1. Lunn JK, Dannemiller FJ, Stanley TH: Cardiovascular responses to clamping of the aorta during epidural and general anesthesia. Anesth Analg 58:372–376, 1979
2. Sadjadpour K: Hazards of anticoagulation therapy shortly after lumbar puncture. JAMA 237:1692–1693, 1977
3. Bamford CR: Spinal epidural hematoma due to heparin. Arch Neurol 35: 693, 1978
4. DeAngelis J: Hazards of subdural and epidural anesthesia during anticoagulant therapy: a case report and review. Anesth Analg 51:676–679, 1972
5. Janis KM: Epidural hematoma following postoperative epidural analgesia: case report. Anesth Analg 51:689–692, 1972
6. Varkey GP, Brindle GF: Peridural anaesthesia and anticoagulant therapy. Can Anaesth Soc J 21:106–109, 1974

To the Editor:

It was not the purpose of our paper[1] to advocate or condemn epidural or general anesthesia in patients undergoing major aortic surgery (in which anticoagulation is required) but rather to describe cardiovascular responses to aortic clamping and unclamping with different forms of fluid therapy. However, Dr. McCullough's letter raises a pertinent and important issue, the advisability of using continuous epidural anesthesia in patients who are going to receive anticoagulant therapy during surgery. There are, as he points out, a number of reports in the literature that indicate that epidural hematoma is a complication of this technique when anticoagulation is used during or even after removal of the epidural catheter.[2-5] Furthermore, epidural hematoma in these situations is often associated with serious neurologic damage, especially when the hematoma is not recognized early and promptly evacuated.[2, 3] As a result of these potentially serious risks, it has been recommended by some that continuous epidural anesthesia be avoided whenever possible if anticoagulants are likely to be used during surgery. This recommendation is rational and, indeed, may be the safest, most conservative form of anesthetic care in these patients. On the other hand, the incidence of epidural hematoma formation in patients with catheters in their epidural space who are subsequently given anticoagulants is unknown. Since spontaneous epidural hematoma formation is a well recognized complication of any form of anticoagulation therapy,[6] it is possible that the presence of a catheter in the epidural space at the time of anticoagulation has little to do with the subsequent formation of an epidural hematoma. Again, unfortunately, to our knowledge, no data are available to indicate that the incidence of hematoma formation is any greater in patients with a catheter in their epidural space who are given anticoagulants during operation and then have the catheter removed after operation when their coagulation profile has returned to normal, than it is in patients who are given anticoagulants without a catheter in their epidural space. Since patients often receive anticoagulation therapy of some form during a variety of surgical procedures today (in many, continuous epidural anesthesia is, for a variety of reasons, the anesthetic of choice), to condemn use of an epidural catheter in these patients seems irrational especially considering the lack of incriminating evidence available.

None of the above should be understood to imply that anything but the greatest care must be taken in the placement, securement, and removal of epidural catheters in patients who are to receive or have already received anticoagulants. It is well known that epidural catheters can cause hemorrhage in the epidural and/or subarachnoid space during placement and removal. It is our policy not to use continuous epidural anesthesia in a patient who is already receiving anticoagulants. We also remove the catheter and do not use continuous epidural anesthesia in a patient who is to be given anticoagulants during surgery if the introduction of the catheter results in a traumatic tap. We feel it is important to ensure that all heparin activity is neutralized (via frequent activated clotting time analyses) prior to removal of the epidural catheter postoperatively. Since our hospital is a teaching institution and operations may take many hours, the time interval between placement of the epidural catheter and initial heparinization is of little importance (in the cases we reported[1] this interval ranged between 90 and 170 minutes).

In order to diagnose rapidly and treat any epidural hematoma that might occur in spite of all our precautions (we have, up to this time, no evidence that any has ever occurred) all patients are returned to the intensive care unit after surgery where, in addition to the usual cardiovascular, respiratory, and renal function monitoring, periodic neurologic examinations are performed and the back intermittently inspected. Until clearly demonstrated otherwise, it appears to us that continuous epidural anesthesia is a safe and rational technique in patients who might benefit from regional anesthesia in aortic or other operative procedures in spite of subsequent anticoagulation during operation, if reversal of anticoagulant activity is achieved prior to epidural catheter removal and careful monitoring is practiced in the recovery room or intensive care unit.

Theodore H. Stanley, MD
Judd K. Lunn, MD
*Department of Anesthesiology*
*University of Utah Medical Center*
*Salt Lake City, Utah 84132*

REFERENCES

1. Lunn JK, Danemiller FJ, Stanley TH: Cardiovascular responses to clamping of the aorta during epidural and general anesthesia. Anesth Analg 58:372–376, 1979
2. De Angelis J: Hazards of subdural and epidural anesthesia during anti-coagulant therapy: a case report and review. Anesth Analg 51:676–679, 1972
3. Janis KM: Epidural hematoma following post-operative epidural analgesia: case report. Anesth Analg 51:689–692, 1972
4. Gingrich TF: Spinal epidural hematoma following continuous epidural anesthesia. Anesthesiology 29:162–163, 1968
5. Varkey GP, Brindle GF: Peridural anesthesia and anti-coagulant therapy. Can Anaesth Soc J 21:106–109, 1974
6. Markham JW, Lynge HW, Stahlman EBS: The syndrome of spontaneous spinal epidural hematoma: report of 3 cases. J Neurosurg 26:334–340, 1967

# book REVIEWS

## Renal Function in Anaesthesia and Surgery, by D. R. Bevan, New York, Grune & Stratton, Inc (London Edition for Americas from Academic Press), 1979, 239 pp, $35.00.

Dr. Bevan outlines the intent of his book in the preface: "Part of the purpose of this book is to review those advances (in knowledge of renal function) which are relevant to anaesthetists and surgeons involved with the clinical care of the patient with threatened or existing renal dysfunction during the operative period. In addition, the effects of anaesthesia and surgery upon renal function are discussed." This monograph is intended for surgeons and anesthesiologists, and is not limited to a discussion of renal function during anesthesia and surgery. The approximately 180 pages of text are divided into three sections: Basic Principles (pp 3-84); Renal Function During Anaesthesia and Surgery (pp 87-128); and Renal Failure (pp 131-180). The first section reviews renal anatomy, circulation, and function, as well as "Drugs and the Kidney" and "Renal Function Tests." The second section is subdivided into: "Anaesthesia and the Kidney" (20 pp); "Methoxyflurane Nephrotoxicity," which also refers to fluoride aspects of enflurane, isoflurane, sevoflurane, and fluroxene metabolism (10 pp); and "Surgery and the Kidney" (10 pp). The final 50 pages discuss pathogenesis and management of renal failure, including aspects of anesthetic management of patients with chronic renal failure. The bibliography is relatively extensive and current. Appropriate tables and black and white illustrations are included in the text.

To cover such a range of subject matter in a monograph of this size necessitates that the writer present capsule summaries of topics, generally in the form of a series of statements, with little discussion. The reader is directed to the references to pursue topics of interest. Such is the price of brevity. An additional disadvantage in this monograph is that the author does not always indicate whether the work he is summarizing was done in animals or in man.

This book provides a useful current summary of renal function for surgeons and anesthesiologists. With the exception of portions of the first chapter, where somewhat complex sentence structure coupled with the brevity of the presentation slows the reader, the text is relatively easy to read. The book's title may lead some readers to anticipate learning more about renal function associated with anesthesia and surgery, and less about basic principles of renal physiology than the text provides.

Overall, this monograph would be a useful addition to an anesthesiologist's library.

Joseph M. Messick, MD
Associate Professor
of Anesthesia
Mayo Medical School
Rochester, MN

## International Anesthesiology Clinics, Volume 17, edited by B. A. Britt, Boston, Little, Brown & Co., 182 pp, $35.00.

Dr. Britt has gathered reviews from certain of the foremost investigators of malignant hyperthermia (MH) to "provide information which will assist anesthesiologists in detection of MHS [malignant hyperthermia syndrome] individuals before surgery; providing safe anesthetic techniques; making early diagnosis during an acute crisis; and managing MH reactions effectively." Most of these goals are achieved if it is considered that the number of unanswered questions regarding MH far exceeds the answered questions. The first and final chapters provide concise and thorough outlines for identifying and treating the acute MH crisis. Therapeutic guidelines are presented in a usable outline form. The therapeutic value of procainamide is overemphasized while that of dantrolene sodium is understated, probably as a consequence of the unavailability of studies using intravenous dantrolene at the time of writing. A chapter on the etiology and pathophysiology resounds the increased myoplasmic $Ca^{2+}$ theory as the primary etiologic event, and clinical evidence is cited to suggest that defective $Ca^{2+}$ regulating membranes may not be limited only to skeletal muscle. A chapter on porcine MH provides an excellent review of MH pathogenesis in the animal model and the potential relationships to MH in man. A chapter describing extensive studies on skeletal and heart muscle, motor nerves, bone, and platelets as elective diagnostic techniques may leave the reader wondering how any patient may escape a positive diagnosis. Dr. Britt finally concedes that a definitive diagnosis for the individual patient depends upon contracture testing of a skeletal muscle biopsy. Certain new and thought-provoking theories are presented in a chapter on possible genetic and environmental factors which predispose to an occurrence of MH. Evidence is cited for a multifactorial mode of inheritance. A thorough scheme of anesthesia for MHS patients is presented in detailed, protocol form. The book is recommended as a summary of some recent advances in MH research and details for clinical management.

T. E. Nelson, PhD
Assistant Professor
Department of Anesthesiology
University of Texas Medical
Branch
Galveston, TX

---

## **Anaesthesia for Children,** by T.C.K. Brown and G.C. Fisk, Oxford, Blackwell Scientific Publications, 1979, 439 pp, $77.50.

This new textbook from Australia is impressive and well prepared. It is, for the anesthesiology resident, a source of theory. For the practitioner, it is a reference for practical application. From the foreword by Gordon Bush to the chapters devoted to Basic Anatomy, Physiology, Pharmacology, Equipment, Special Surgical Specialties, Medical Disease, Special Emergencies, Outpatient Procedures, and Intensive Care, it is an outstanding work on contemporary pediatric anesthesia.

The photographs are well done and truly descriptive of many of the techniques of pediatric anesthesia. The emphasis on intravenous equipment and its use is an example of the thorough nature of this book. Techniques related to endotracheal tubes are well supplemented with photographs.

For specific surgical specialties, the chapters are presented with considerations of the preoperative preparation, principles of anesthetic management, and specific conditions. Additionally, included are the radiologic procedures with theoretical and technical considerations for pneumoencephalography, myelography, cerebral angiography, computerized axial tomography, bronchography, and cardiologic investigations. Included in all these chapters are the anesthetic options of anesthetic agents and techniques.

The chapter dealing with regional and local anesthesia is well outlined; the chapter on outpatient anesthesia is limited. Information related to fluid, electrolyte, and acid base abnormalities is well referenced.

This book is devoted to pediatric anesthesia. It makes no pretext of in-depth consideration of general physiology or pharmacology. It meets its title objective as a reference and working book of anesthesia for children.

E. Warner Ahlgren, MD
Chairman
Department of Anesthesiology
Scott and White Clinic
Temple, TX

---

## **Acupuncture Manual, A Western Approach,** by L.S.W. Chu, S.D.J. Yeh, and D.D. Wood, New York, Marcel Dekker, Inc, 1979, 256 pp, $15.00.

In *Acupuncture Manual, A Western Approach*, the authors have attempted to blend the 5000-year old pragmatic Oriental healing art with 20th century Western medical science.

The manual devotes a chapter to current research in acupuncture with experimental results in basic and clinical sciences. Much of acupuncture's magical past is brought into perspective in this book. Pain mechanisms related to Western medicine are given emphasis by relating them to the neurophysiologic and endogenous analgesic peptide system. In addition, physiologic studies of certain nonpainful states that may respond to acupuncture are also presented. This includes acupuncture's effect on the gastrointestinal tract, respiratory system, as well as hematologic and endocrine systems. This information is valuable because it gives an overall idea of how and where acupuncture may fit into Western clinical practices. Thankfully, there is a welcome departure from the traditional theory of yin and yang and the philosophical explanations of its mechanisms; instead this book emphasizes how acupuncture may prove effective if prescribed and practiced properly.

The manual includes the most important loci for treatment of specific problems, whether they are pain problems or other physiologic conditions that may or may not occur with accompanying pain. These have been shown to respond to acupuncture by pragmatic observation over many years.

These important loci of the acupuncture anatomical system are illustrated and referred to by specific anatomical locations, both by traditional Eastern methods as well as modern Western approaches.

The newer acupuncture developments and techniques, including scalp acupuncture, auriculoacupuncture, as well as the surgical suture embedding technique are also presented.

There is a formulary for acupuncture analgesia for surgical procedures. I believe that this is of limited value in Western medicine, perhaps, with the exception of head and neck areas.

The cross-indexing of loci is commendable because it clarifies the confusion by the many acupuncture labeling systems. It would have been nice to have these loci cross-indexed in the manual's subject index.

Also a correction sheet for the minor typographical errors and grammar should have been supplied. All in all, the positives outweigh the negatives, and I feel that this manual will prove valuable for the Western trained health care professional who is seeking minimally invasive approaches to certain pain and physiologic problems of patients seen in day-to-day practice.

Richard Kroening, MD, PhD
Assistant Professor
Pain Management Clinic
Medical Director
TMJ & Facial Pain Clinic
University of California
Los Angeles, CA

---

## **Blood Gases and Acid-Base Physiology,** by N. L. Jones, New York, Brian C. Decker, 1980, 175 pp.

This comprehensive and informative programmed text asks and answers a series of questions directed toward a basic knowledge of pulmonary gas exchange and acid-base physiology. The reader is initially challenged with a problem in interpretation of blood gas measurements and then led through a very complete basic discussion of pulmonary gas exchange. A three-component model is explored. Entry components, gas exchange component, and exit components are defined, and an "ideal" compartment (ventilation and perfusion equals diffusion block) of venous admixture and a dead space compartment are described. Alveolar ventilation and $CO_2$ output are discussed; respiratory dead space measurements are described; the alveolar gas equation is then derived and alveolar-arterial oxygen tension differences ($P(A\text{-}a)O_2$) are discussed. Oxygen transport and cardiac ouput are then linked through the Fick equation.

The concept of venous admixture is described in detail and the three-compartment model is expanded to include $\dot{V}/\dot{Q}$ mismatching. Finally, $P(A\text{-}a)O_2$ and venous admixture ($\dot{Q}_S/\dot{Q}_T$) are compared as estimates of inefficiency of gas exchange. The carriage of carbon dioxide is then described but in somewhat less detail. The carriages of oxygen and carbon dioxide are compared and the effects of $\dot{V}/\dot{Q}$ again briefly explored. In the second part of the book, acid-base physiology is described in a fairly conventional manner. This basic introduction leads into detailed discussion of some clinical problems.

Appendices include sections on arterial blood sampling and blood gas measurement techniques, the physics of gases, the international system of units, and finally the $O_2$-$CO_2$ diagram, which is explained in some detail.

The acid-base section in this book is shorter than, but is similar in some ways to, those in a number of other short books currently on the market, notably the later editions of Davenport's, *The ABC of Acid-Base Chemistry*, which also gives a short section on oxygen transport, Gösta Rooth's *Acid Base and Electrolyte Balance*, and Schwartz and Lyons', *Acid-Base Balance and Electrolyte Balance: Normal Regulation and Clinical Disorders.* Jones' book differs in that it is designed as a teaching tool with programmed text and introductory and final evaluations. This may make it particularly useful in introducing the subject to students. It would make a useful companion volume to West's two texts, *Respiratory Physiology—The Essentials* and *Respiratory Pathophysiology* Thus, the book is recommended either as a useful introduction to the subject or for rapid review and renewal for those with more advanced knowledge.

H. Michael Marsh, MB
Assistant Professor
of Anesthesia
Mayo Medical School
Rochester, MN

## BOOK NOTES

### Illustrated Handbook in Local Anaesthesia, edited by E. Eriksson, Philadelphia, W. B. Saunders Co., 1980, 159 pp, $37.50.

The stated objective of this book is to provide a small book on regional anesthesia with good drawings, illustrative pictures, and a short text for practical clinical work. This goal has been admirably achieved.

This book differs from the first edition only slightly; a few drawings and topics have been added or removed but there is not enough change to warrant discarding the first edition.

The outstanding features of this book are the excellent illustrations, with brief and to-the-point copy. It would be an excellent addition to the library of anyone interested in regional anesthesia.

### A Primer of Water, Electrolyte and Acid-Base Syndromes, Sixth edition, by E. Goldberger, Philadelphia, Lea & Febiger, 1980, 472 pp, $18.50.

The sixth edition of this 20-year-old classic retains the short chapters, terse discussion, and clinical correlations which no doubt account for its longevity. Values are expressed in metric units with very rare use of Systeme Internationale terminology, and the use of tables and graphs is held at a minimum. The Siggaard-Andersen nomogram is retained and used in the calculation of bicarbonate, but in general the additions and deletions have appropriately updated this edition.

## BOOKS RECEIVED

**Anesthesia and the Patient with Heart Disease,** edited by B. R. Brown, Jr., Philadelphia, F. A. Davis Co., 1980, 193 pp, $20.00.

**Hemotherapy in Trauma and Surgery,** by The Committee on Workshops of The American Association of Blood Banks, Washington, DC, American Association of Blood Banks, 1979, 88 pp, $10.00.

**Platelet Physiology and Transfusion,** by The Committee on Workshops of The American Association of Blood Banks, Washington, DC, American Association of Blood Banks, 1978, 92 pp, $15.00.

**Pediatric Anesthesia Handbook, Second edition,** by R. M. Levin. Garden City, NY, Medical Examination Publishers, 1979, 364 pp, $13.75.

**Self-Assessment of Current Knowledge in Anesthesiology,** by D. L. Trickey, Garden City, NY, Medical Examination Publishers, 1980, 200 pp.

# I.A.R.S. MEMBERSHIP

## For Your In-training and Continuing Medical Education

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio founded in 1922 "To Foster Progress and Research in Anesthesia." To this end it performs two functions: (1) Publication of monthly journal, ANESTHESIA and ANALGESIA; and (2) Sponsorship of annual scientific "Congress" meetings which meet the criteria for Category 1 credit toward the AMA Physicians Recognition Award.

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state or national anesthesia organizations.

## MEMBERSHIP - ASSOCIATE MEMBERSHIP

MEMBERSHIP is open to individuals with doctorate degrees, licensed to practice in the medical, dental, osteopathic or veterinary medicine professions (i.e., MD, MB, DDS, DMD, DO, DMV); and to individuals with doctorate degrees (Ph.D.) in any scientific discipline, engaged in academic, private or commercial research.

ASSOCIATE MEMBERSHIP is open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA), respiratory therapists (RRT), or respiratory technicians (CRTT); and individuals completing accredited training programs as physician assistants-anesthesia, physician associates in anesthesiology, or as anesthesiologist's assistants.

DUES are $30 per year for U.S. Members and Associate Members, ($33 for all others) and include a subscription to ANESTHESIA and ANALGESIA. Members are also entitled to reduced registration fee at IARS annual scientific meetings.

## EDUCATIONAL MEMBERSHIP

EDUCATIONAL MEMBERSHIP is open to residents and fellows (interns) enrolled in anesthesiology training programs; registered nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician (anesthesiologist) assistants (associates); or students enrolled in respiratory therapist or technician training programs.

The official Education Membership blank must be certified by the applicant's training program director.

DUES are $30 for a two-year period, or $45 for a three-year period, and include a subscription to ANESTHESIA and ANALGESIA for a corresponding period. Educational Members are entitled to complimentary registration at IARS annual scientific meetings.

Application forms for Membership are available upon request to the Cleveland business office per application form below.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122, U.S.A.

Please send me application for: (____) Membership
(____) Associate Membership
(____) Educational Membership

(____) Please send ________ Educational Membership applications for students in anesthesia training.

(Name)

(Address)

(City, State, Zip)

# A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

## Editorial Policies

Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

**Types of materials.** The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

**Peer review.** All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

**Legal and ethical considerations.** Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

**Editing.** All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

## Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

**Title Page.** The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

**Abstract and Key Words.** The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Define all abbreviations except those approved by the International System of Units.

*Key (indexing) terms.* Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract.

**Text.** The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

*Introduction.* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods.* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

*Results.* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

*Discussion.* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**References.** (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus*. Consult the "List of Journals Indexed," printed annually in the January issue of *Index Medicus*.

Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

*Journal*

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

*Books and Other Monographs*

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

**Tables.** Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, †† . . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

**Illustrations.** Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of *original* drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 12.7 by 17.3 cm (5 by 7 in) but no larger than 20.3 by 25.4 cm (8 by 10 in). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them using paper clips. Do not bend figures.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with background.

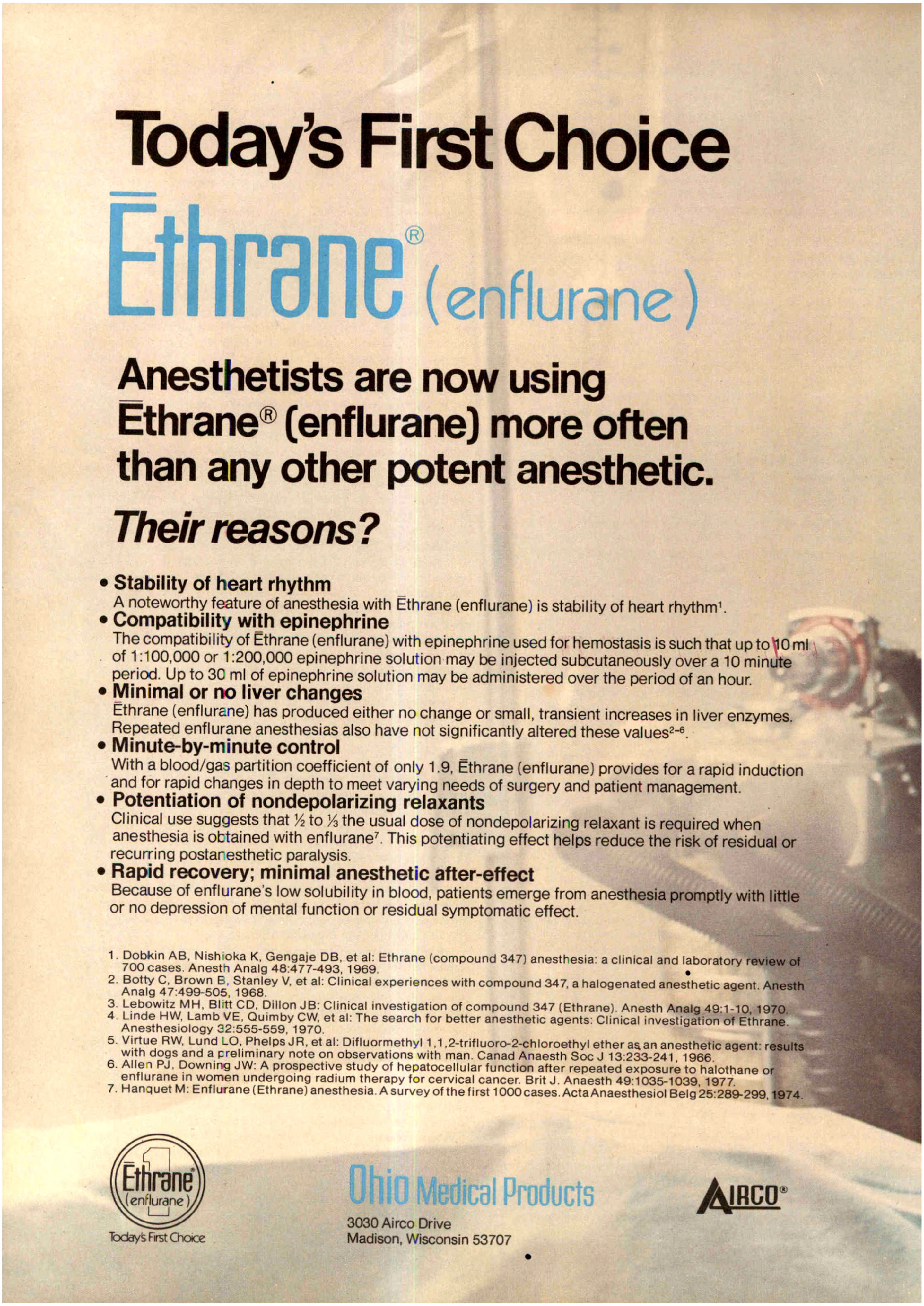
If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, *regardless of authorship or publisher*, except for documents in the public domain.

For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Some journals publish illustrations in color only if the author pays for the extra cost.

**Legends for Illustrations.** Type legends for illustrations double spaced, starting on a separate page with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

**Abbreviations.** Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.



# Today's First Choice

# Ēthrane® (enflurane)

## Anesthetists are now using Ēthrane® (enflurane) more often than any other potent anesthetic.

## *Their reasons?*

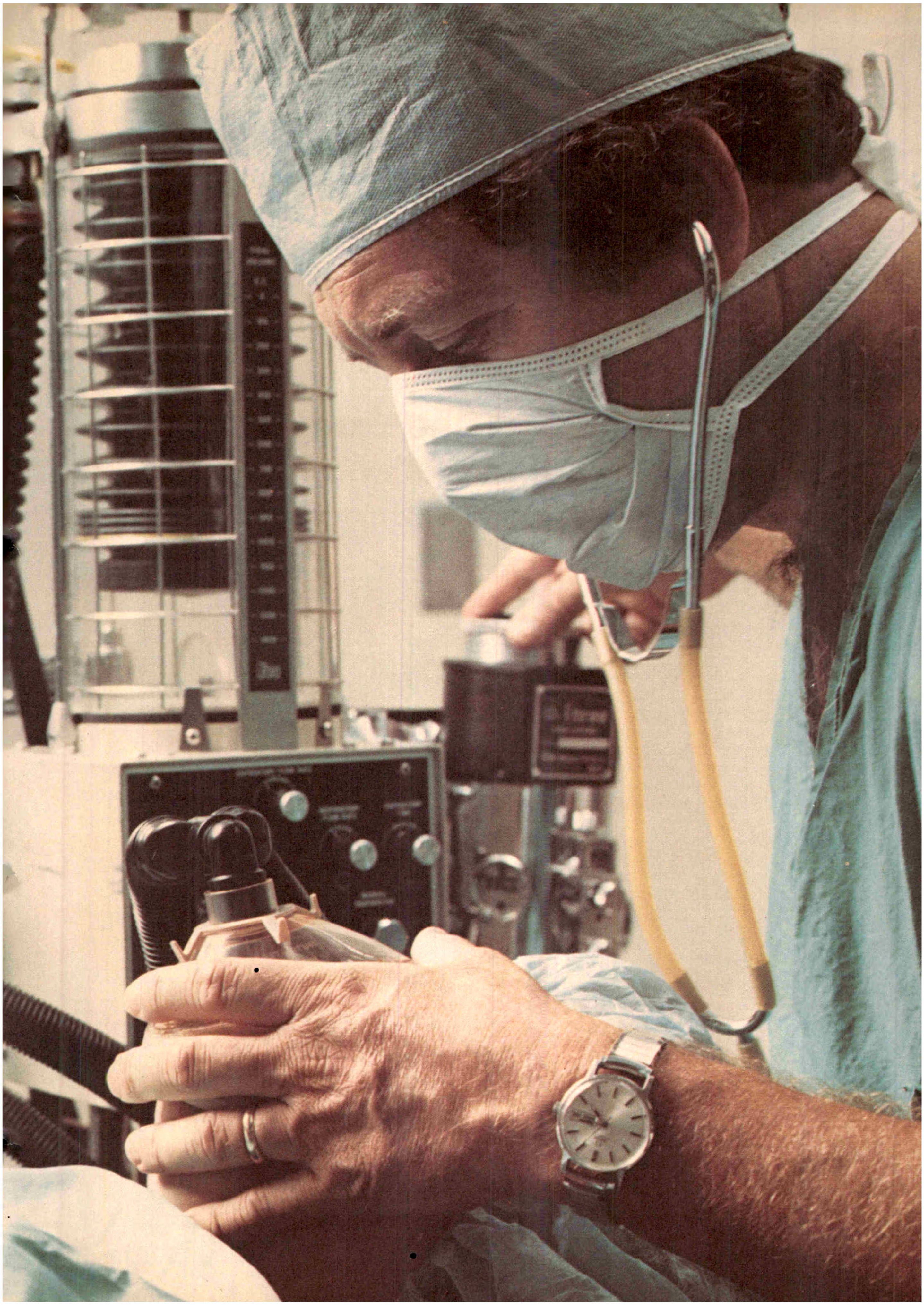
- **Stability of heart rhythm**
  A noteworthy feature of anesthesia with Ēthrane (enflurane) is stability of heart rhythm[1].
- **Compatibility with epinephrine**
  The compatibility of Ēthrane (enflurane) with epinephrine used for hemostasis is such that up to 10 ml of 1:100,000 or 1:200,000 epinephrine solution may be injected subcutaneously over a 10 minute period. Up to 30 ml of epinephrine solution may be administered over the period of an hour.
- **Minimal or no liver changes**
  Ēthrane (enflurane) has produced either no change or small, transient increases in liver enzymes. Repeated enflurane anesthesias also have not significantly altered these values[2-6].
- **Minute-by-minute control**
  With a blood/gas partition coefficient of only 1.9, Ēthrane (enflurane) provides for a rapid induction and for rapid changes in depth to meet varying needs of surgery and patient management.
- **Potentiation of nondepolarizing relaxants**
  Clinical use suggests that ½ to ⅓ the usual dose of nondepolarizing relaxant is required when anesthesia is obtained with enflurane[7]. This potentiating effect helps reduce the risk of residual or recurring postanesthetic paralysis.
- **Rapid recovery; minimal anesthetic after-effect**
  Because of enflurane's low solubility in blood, patients emerge from anesthesia promptly with little or no depression of mental function or residual symptomatic effect.

1. Dobkin AB, Nishioka K, Gengaje DB, et al: Ethrane (compound 347) anesthesia: a clinical and laboratory review of 700 cases. Anesth Analg 48:477-493, 1969.
2. Botty C, Brown B, Stanley V, et al: Clinical experiences with compound 347, a halogenated anesthetic agent. Anesth Analg 47:499-505, 1968.
3. Lebowitz MH, Blitt CD, Dillon JB: Clinical investigation of compound 347 (Ethrane). Anesth Analg 49:1-10, 1970.
4. Linde HW, Lamb VE, Quimby CW, et al: The search for better anesthetic agents: Clinical investigation of Ethrane. Anesthesiology 32:555-559, 1970.
5. Virtue RW, Lund LO, Phelps JR, et al: Difluormethyl 1,1,2-trifluoro-2-chloroethyl ether as an anesthetic agent: results with dogs and a preliminary note on observations with man. Canad Anaesth Soc J 13:233-241, 1966.
6. Allen PJ, Downing JW: A prospective study of hepatocellular function after repeated exposure to halothane or enflurane in women undergoing radium therapy for cervical cancer. Brit J. Anaesth 49:1035-1039, 1977.
7. Hanquet M: Enflurane (Ethrane) anesthesia. A survey of the first 1000 cases. Acta Anaesthesiol Belg 25:289-299, 1974.

Ēthrane® (enflurane)
Today's First Choice

Ohio Medical Products
3030 Airco Drive
Madison, Wisconsin 53707

AIRCO®

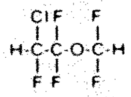


# Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

## DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$\mathrm{H{-}CClF{-}CF_2{-}O{-}CF_2{-}H}$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \quad A = 7.967$$
$$B = -1678.4$$
$$T = {}^\circ C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

## ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High $pCO_2$ levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of phecchromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

## INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

## CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

## WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

## PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

## ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

## DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

**Induction:** Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

**Maintenance:** Surgical levels of anesthesia may be obtained with 1.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

**Overdosage:** In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

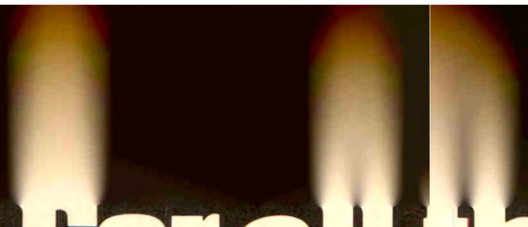
Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

## PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

**Ohio Medical Products**
Division of Airco Inc.
P.O. Box 7550, 3030 Airco Drive, Madison, Wis. 53707

AIRCO®



# For all three,

**In neonatal ventilation,** *"I need a small, constant, compressible volume for greater accuracy and consistency of tidal volume delivery."*

**In adult ventilation,** *"I need low resistance to gas flow to minimize the work of breathing for the patient during IMV and CPAP."*

**In anesthesia,** *"I need high heat and humidity output to maintain the patient's body temperature during prolonged surgical procedures."*

# one answer. Bird.

Many demands are made on a heated humidifier. The Bird Heated Humidifier meets them fully. It outperforms all others in recent comparative studies.* Only Bird:

- Has the lowest consistent compressible volume (180 ml)
- Offers the lowest resistance to gas flow (0.3 cm$H_2O$/L/sec at 60 LPM)
- Delivers 100% RH at 37°C at high gas flows
- Exhibits the smallest temperature variation over a 10-hour observation period

Other proven features can be added to this tested performance:

- Speed: the fastest warm-up time of just 2½ minutes
- Patient safety: built-in audible/visual high temperature alarm. LCD monitor display of proximal airway temperature
- Compact size and quiet operation

Compare it, as others have, and you'll discover that no other heated humidifier offers so much.

*Data on file, Bird Corporation.

**Bird Corporation**
Mark 7
Palm Springs, California 92263
(714) 327-1571

3M

# *Anesthesia and Analgesia*

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | 4 | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | 4 | 5 | 6 |
| 36 | 1957 | – | 2 | – | – | – | 6 | 44 | 1965 | – | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | 3 | 4 | 5 | 6 |
| 38 | 1959 | – | 2 | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | 5 | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | 2 | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | 3 | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | 4 | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | – | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | 3 | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 |
| 59 | 1980 | 1 | | | | | |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.
BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955
OTHER PUBLICATIONS AVAILABLE:

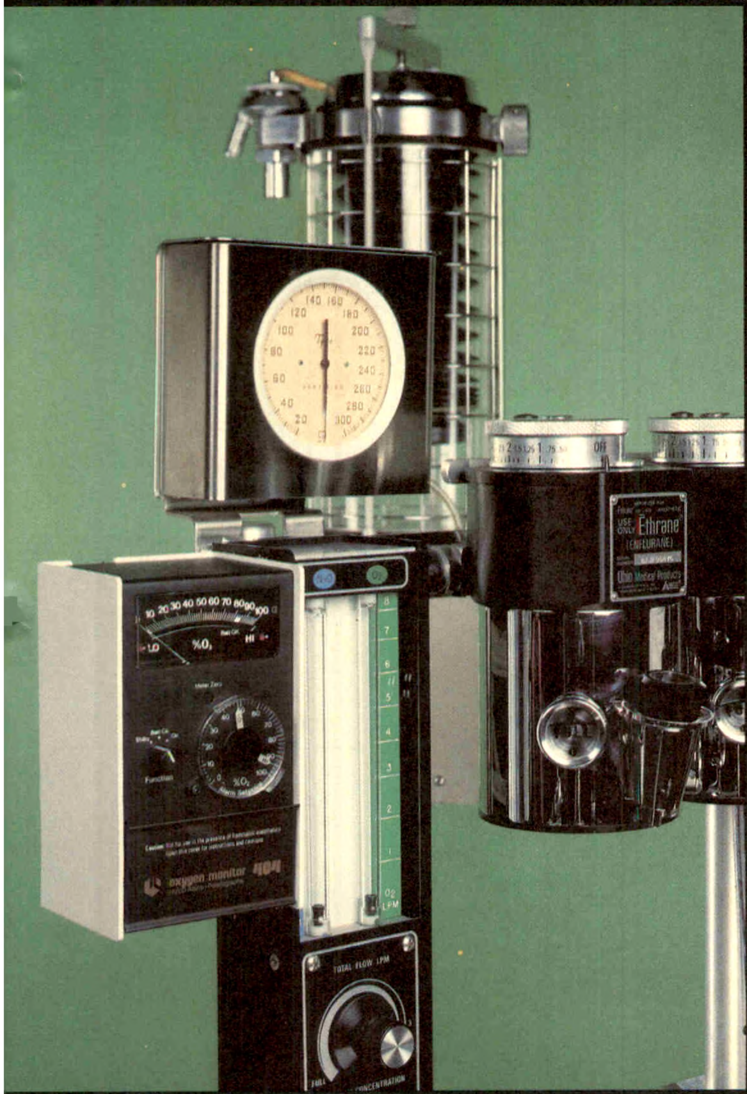
"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.
Ten-Year (1960-1969) Cumulative Index—$3.00.
Ten-Year (1970-1979) Cumulative Index—$3.00.
1979 (53rd Congress) Review Course Lectures—$5.00.
1980 (54th Congress) Review Course Lectures & Abstracts—$5.00.

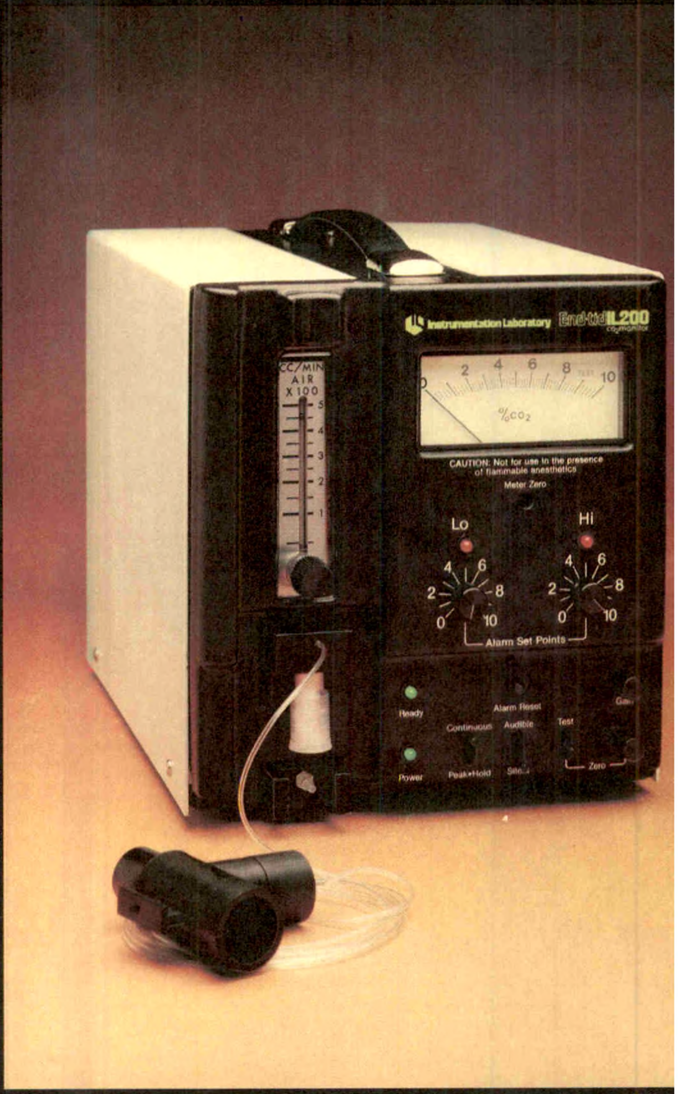
International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122
Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.
☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name ______________________________
Address ______________________________
City, State, Zip ______________________________

Monitor the ins *and* the outs of ventilation.





The new **End-tidIL™ 200 $CO_2$ Monitor** gives you breath-by-breath analysis of expired $CO_2$ at an affordable price.

For over a decade, IL has been providing anesthesiologists with products to monitor oxygen delivery. Now, the End-tidIL™ 200 $CO_2$ Monitor provides a safeguard for proper ventilation. At an introductory price of under $2000.

This new instrument monitors the patient's expired % $CO_2$ on a continuous or peak value basis to indicate:

- cardiac and pulmonary information
- hypercapnia and hypocapnia
- malfunction of the $CO_2$ absorber
- air embolism
- disconnected or obstructed airway
- changes in arterial $P_{CO_2}$

IL, the leading manufacturer of $O_2$ Monitors, offers this quality $CO_2$ Monitor at a price that makes it affordable for every patient under anesthesia to be assured of proper ventilation. For a demonstration or further information, call IL toll-free: **800 225-4040**
(800 342-8856 in MA)
or write:

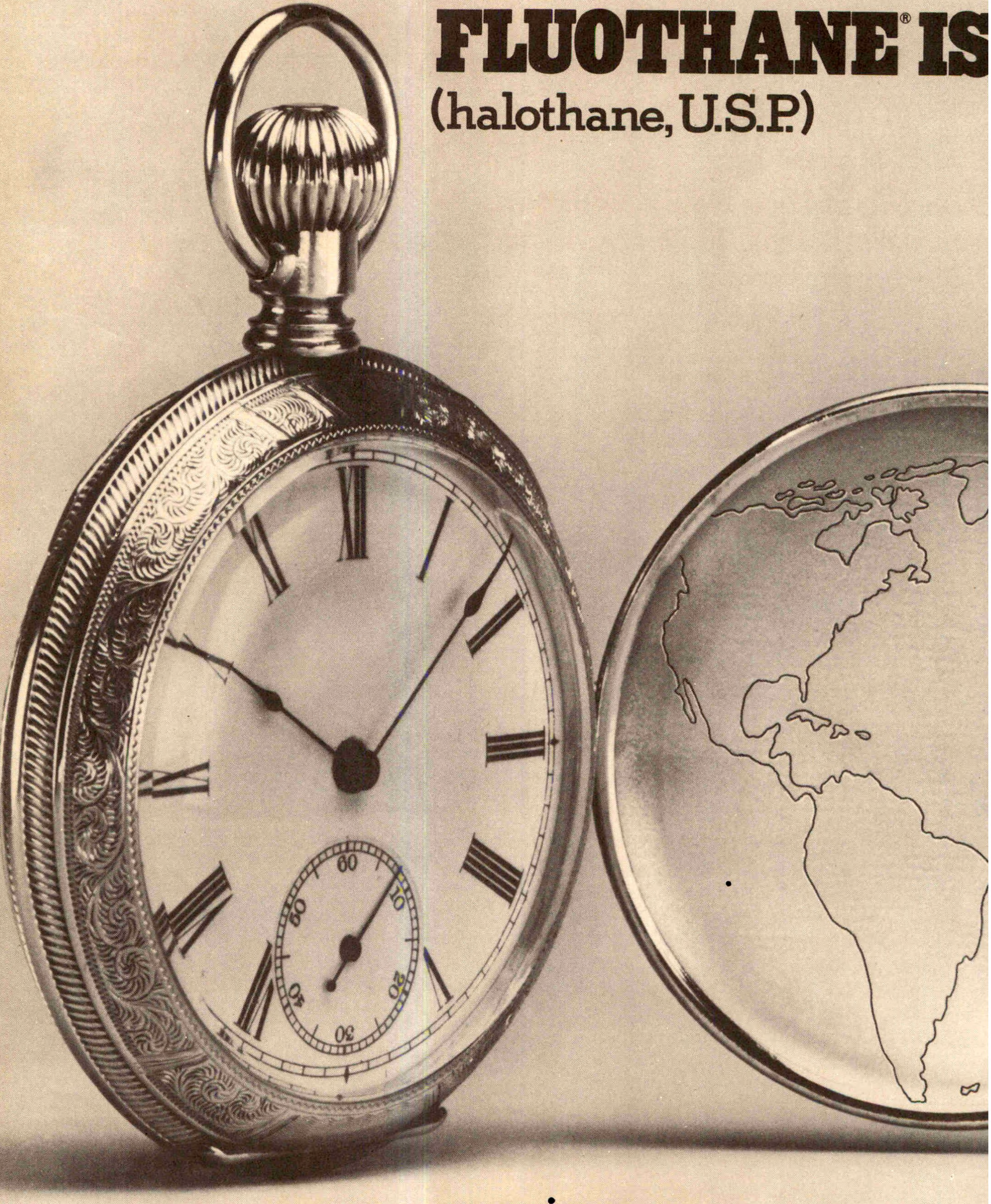
The Critical Care Specialist...
Instrumentation Laboratory Inc.
Sensorlab Division
One Burtt Road
Andover, MA 01810

Instrumentation Laboratory

# EVERY TWO SECONDS

# FLUOTHANE® IS

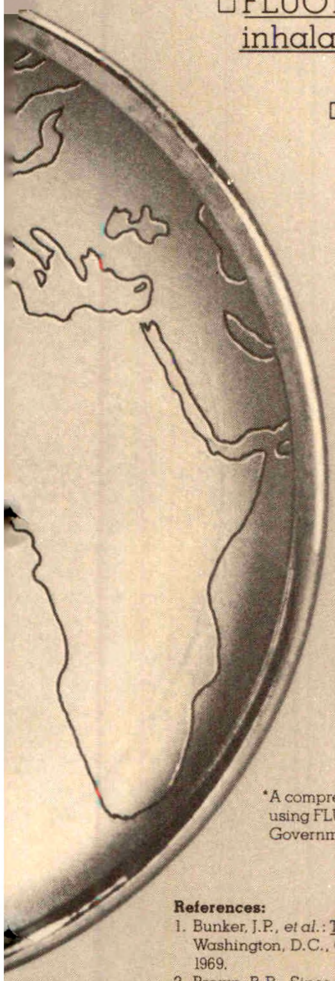
(halothane, U.S.P.)



# THE WORLDWIDE CHOICE.

## Over 500 million administrations throughout the world. Well over 125 million administrations in the United States alone.

Somewhere in the world—every two seconds—someone makes another decision to use FLUOTHANE® (halothane, U.S.P.). And for good reasons:



☐ FLUOTHANE has been more widely investigated than any other inhalation anesthetic.

☐ The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and... the overall safety record of the anesthetic was excellent."[2]

☐ FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]

☐ FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.

☐ And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

---

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

**References:**

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. *26*:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology *43*:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

Ayerst®
Ayerst Laboratories
New York, N.Y. 10017

# the most widely used inhalation anesthetic in the world

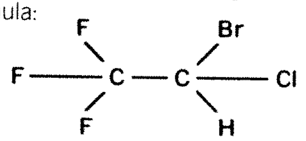
# FLUOTHANE®

## (halothane, U.S.P.)

## for a wide variety of techniques and procedures in patients of all ages

*(Complete text of package circular.)*

**Description.** FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

**Actions.** FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

**Indications.** FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

**Contraindications.** FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

**Warnings.** When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

*Usage in Pregnancy.* Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

**Precautions.** The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

**Adverse Reactions.** The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

**Dosage and Administration.** FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

**How Supplied.** No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P. stabilized with 0.01% thymol (w/w).

**Ayerst.** Ayerst Laboratories
New York, N.Y. 10017

7197/80

When you have the best Epidural Catheter, You design the best Continuous Epidural Anesthesia Tray.

**Introducing the Portex Continuous Epidural Anesthesia Tray featuring the Exclusive Portex Nylon Catheter.**

All the necessary components for the administration of Continuous Epidural Anesthesia conveniently supplied in a Sterile / Disposable Tray.

Call or write Portex, Inc. or your local Portex, Inc. Distributor for further information and descriptive brochure.

PORTEX®

Portex, Inc. 42 Industrial Way, Wilmington, MA 01887 (617) 658-5110
In Canada: 1361 Huntingwood Drive, Scarborough, Ontario

# classified ADVERTISING

### CRITICAL CARE FELLOWSHIP

Our 300-bed Harvard affiliated teaching hospital has a position available from July 1, 1980 to June 30, 1981 for PGY 4-5 in multi-disciplinary ICU environment. Exposure to all areas of intensive care medicine including invasive and non-invasive monitoring, hyperalimentation, pulmonary care, etc. Specialty alignment not critical but anesthesia experience preferred. Reply to A. Dalal, M.D., Mt. Auburn Hospital, 330 Mt. Auburn Street, Cambridge, MA 02138. Tel: (617) 354-7260. An Equal Opportunity Employer.

### UNIVERSITY OF SOUTH FLORIDA

Chairperson, Department of Anesthesiology, College of Medicine, Tampa. Applicants should be Board Certified, should be capable and experienced in teaching, research and clinical care, and should have leadership and administrative skills appropriate to the development of a new department. Interested candidates should submit inquiries and curricula vitae to Anthony Reading, M.D., Chairman, Anesthesiology Search Committee, Box 14, USF College of Medicine, 12901 N. 30th Street, Tampa, Florida 33612. The University of South Florida is an Equal Opportunity Employer.

### PHYSICIANS WANTED:

University of Alabama in Birmingham, School of Medicine, Department of Anesthesiology has openings for Professor, Associate Professor, Assistant Professor and Instructor to participate in clinical and resident training activities. Applicants may send a C.V. to Edward A. Ernst, M.D., Professor and Chairman, Department of Anesthesiology, University Hospital, University Station, U.A.B., Birmingham, Alabama 35233. An Equal Opportunity/Affirmative Action Employer.

### MARYLAND:

The Maryland Institute for Emergency Medical Services Systems is seeking staff anesthesiologists with an interest and/or experience in critical care, trauma anesthesia and/or neuro-surgical anesthesia/critical care. MIEMSS is the 85 bed clinical center for trauma care and research in the State of Maryland. Teaching and research opportunities in a multidisciplinary setting are available. Salary negotiable, liberal fringe benefits. Send curriculum vitae to: Peter Chodoff, M.D., M.P.H., Chief, Critical Care/Anesthesia, Maryland Institute for Emergency Medical Services Systems, Baltimore, Maryland 21201

### ACADEMIC ANESTHESIOLOGIST POSITION—

Academic anesthesiologists, University of Louisville School of Medicine. Positions for eligible or board certified anesthesiologists with rank commensurate with qualifications. Duties include patient care, medical student and resident teaching, and research. Specific interests may include any subspecialty. Must be eligible for licensure in Kentucky. Inquiry from all qualified applicants welcome. Competitive salary and fringe benefits. Send inquiry, curriculum vitae, and names of four references to George E. Webb, M.D., Chairman, Department of Anesthesiology, P.O. Box 35260, Louisville, Kentucky 40232. An Affirmative Action/Equal Opportunity Employer.

### MAYO FOUNDATION, DEPARTMENT OF ANESTHESIOLOGY—

Opportunities for advanced subspecialty training in cardiovascular and neuro-anesthesia, respiratory intensive care, and pain management are available to qualified candidates. Indepth training experience in one or more of these areas for periods of six months to two years may be arranged. For additional details, contact: Alan D. Sessler, M.D., Chairman, Department of Anesthesiology, Mayo Foundation, Rochester, Minnesota 55901.

### MISSOURI

Anesthesiologist wanted to join private group practice. 400-bed hospital with all specialties except open heart; little OB. Town of 100,000 with good schools, close airport, and good recreation. Excellent starting income, fringes, and potential. Reply to Box 7-79-A, c/o I.A.R.S.

### ANESTHESIOLOGY—

3 year approved Program. All types of Anesthesia—including open heart, inhalation therapy. University affiliated. Please write to: Paul J. Ditmyer, M.D., Chairman; Department of Anesthesiology; The Toledo Hospital; 2142 N. Cove Boulevard; Toledo, Ohio 43606.

### OHIO ANESTHESIOLOGIST—

Position presently available in group comprising M.D.'s and CRNA's in 500 bed hospital with all specialities except open heart. Call or send curriculum to John Biggins, M.D., Dept. of Anesthesia, Trumbull Memorial Hospital, Warren, Ohio 44483. (216) 841-9230.

### PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles has advanced clinical program for residents at the second and third year level of training. Also accepting applications from practicing anesthesiologists who wish to update their knowledge and proficiency. Positions available from 2 months to 1 year. Specialized year approved by the AMA. For further details contact:

George B. Lewis, Jr., MD
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, CA 90027
Phone (213) 662-1708

# classified ADVERTISING

**TULANE UNIVERSITY, New Orleans, Louisiana**

Position available in July 1980 for a staff academic anesthesiologist. Responsibilities in clinical, teaching and research areas. Tulane University is an Affirmative Action/Equal Opportunity employer. Send Curriculum Vitae to: Robert R. Kirby, M.D., Department of Anesthesiology, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112.

**UNIVERSITY OF IOWA, Fellowship in Cardiac Anesthesia:**

Opportunity for excellent training in anesthesia for cardio-vascular and thoracic surgery for anesthesiology trainee seeking SPECIALIZED year position: Offers one year of clinical experience and research involving a wide range of adult and pediatric diseases. For additional details contact: Wendell C. Stevens, Professor and Head, Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242.

*Rates for classified advertising: $3.00 per line, minimum 5 lines; box number ads $3.50 per line. Classified display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia, 3645 Warrensville Center Rd., Cleveland, OH 44122.*

## *CHAIRMAN*
## DEPARTMENT OF ANESTHESIOLOGY

Applications for Chairman of Anesthesia Department at Woodhull Hospital, Brooklyn, NY, are invited. Woodhull, a 640 bed ultra-modern municipal hospital operated by the New York City Health and Hospitals Corporation, will be a primary teaching affiliate of the Downstate Medical School. The hospital, currently under construction is scheduled to open in June of 1981.

Employment will begin six to twelve months prior to the opening date. Applicants must be certified by the American Board of Anesthesiology; have at least five years experience as an attending anesthesiologist; administrative, teaching, and research experiences helpful. *Send curriculum vitae and names and address of three reference persons to:*

James E. Cottrell, M.D., Professor & Chairman,
Department of Anesthesiology,
Downstate Medical Center,
450 Clarkson Avenue, Box 6,
Brooklyn, N.Y., 11203

## FULLY ACCREDITED ANAESTHESIA RESIDENCY PROGRAM
## PGY-1, 2, 3 & 4
### UNIVERSITY of MASSACHUSETTS MEDICAL CENTER

Applications are now being accepted for Anaesthesia Residencies, (PGY-1, 2, 3 & 4) in the Department of Anaesthesia, University of Massachusetts Medical Center, Worcester, Massachusetts. For further information, please contact:

**Michael Stanton-Hicks, M.B.B.S.**
**Program Director of Residency Program**
**Professor and Chairman**
**Department of Anaesthesia**
**University of Massachusetts Medical Center**
**Worcester, MA 01605**

*An Affirmative Action/Equal Opportunity Employer*

**University of Massachusetts Medical Center**

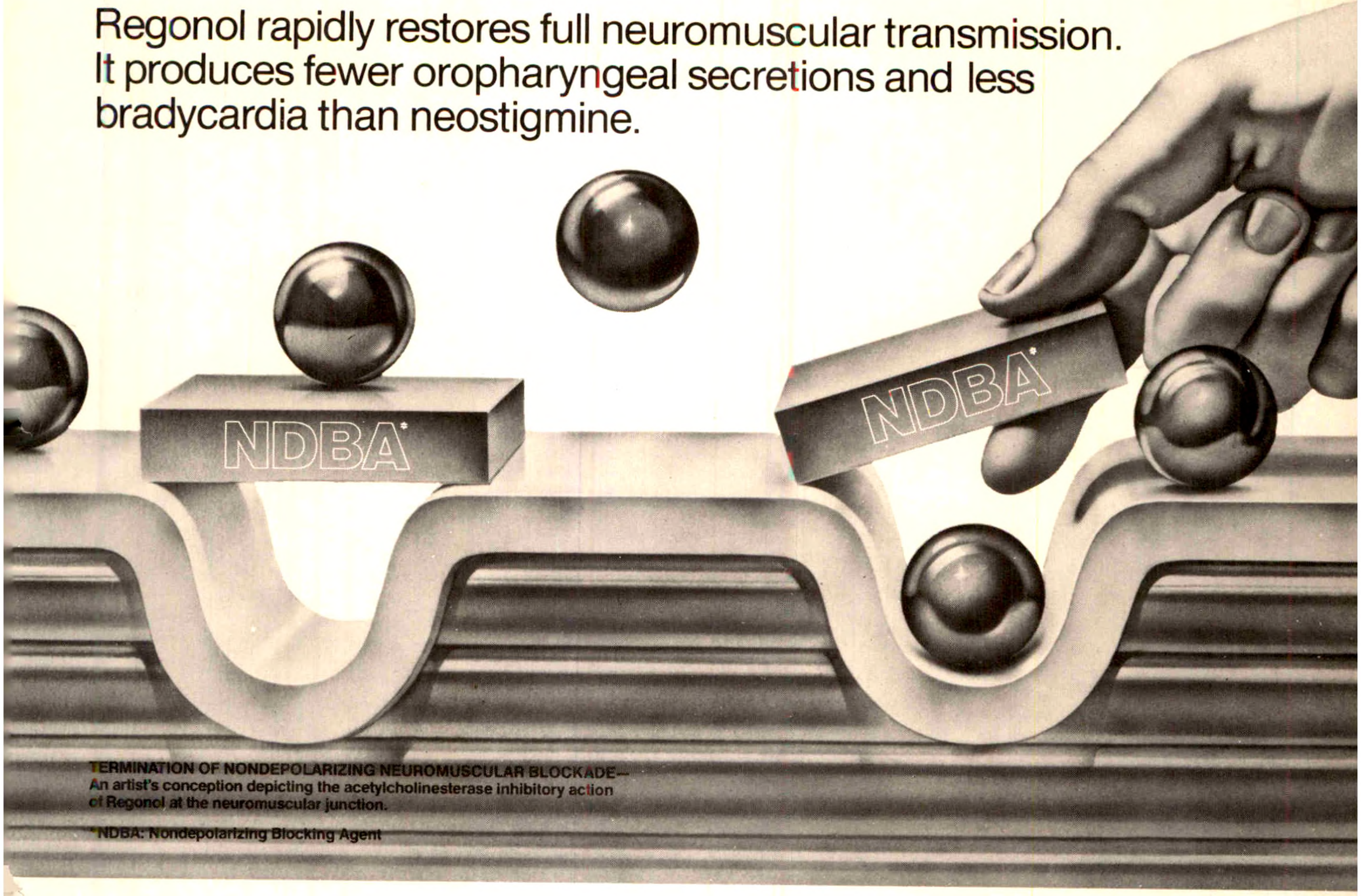
# INDEX OF ADVERTISERS

Ayerst Laboratories—*Fluothane®* . . . (42), (43), (44)
Bird Corporation—*Heated Humidifier* . . . (39)
Bristol Laboratories—*Stadol* . . . (24), (25), (26)
Classified Advertising . . . (46), (47)
J. H. Emerson Company—*IMV Ventilator* . . . (27)
Halocarbon Laboratories, Inc.—*Halothane* . . . (31)
Instrumentation Laboratory—*$CO_2$ Monitor* . . . (41)
Janssen Pharmaceutica, Inc.—*Institutional; Innovar; Sublimaze* . . . (16), (17), (18), (19), (20), (21)
K & G Healthcare Industries, Inc.—*Nicholes II Filter* . . . (28)
KMA, Inc.—*Thermodilution Equipment* . . . (11)
National Catheter Co.—*Esophageal Stethoscope* . . . Cover 2
North American Drager—*Anesthesia Products* . . . (30)
Ohio Medical Products—*Ethrane®* . . . (36), (37), (38)
Ohio Medical Products—*Monitor* . . . (29)
O'Neal, Jones & Feldman—*Antilirium* . . . (22), (23)
Organon Pharmaceuticals—*Hexadrol®* . . . (14), (15)
Organon Pharmaceuticals—*Pavulon®* . . . (4), (5), (6)
Organon Pharmaceuticals—*Regonol®* . . . Cover 3
Pharmaseal®—*Stopcocks and Tubing* . . . Cover 4
Physio-Control Corporation—*CMS 6000* . . . (7)
Portex, Inc.—*Epidural Tray* . . . (45)
Roche Laboratories—*Valium Injectable* . . . (8), (9), (10)
Siemens/Elema AB—*Servo Ventilator Service System* . . . (12), (13)
University of Massachusetts Medical Center—*Employment Opportunity* . . . (47)
Woodhull Hospital, Brooklyn, NY—*Employment Opportunity* . . . (47)

Remove the Block Yourself

# Reverse with REGONOL® pyridostigmine bromide

Regonol rapidly restores full neuromuscular transmission. It produces fewer oropharyngeal secretions and less bradycardia than neostigmine.



**TERMINATION OF NONDEPOLARIZING NEUROMUSCULAR BLOCKADE—**
An artist's conception depicting the acetylcholinesterase inhibitory action of Regonol at the neuromuscular junction.

*NDBA: Nondepolarizing Blocking Agent

**Brief Summary** (Please consult full package insert, enclosed in every package, before using Regonol).

**INDICATIONS**—Regonol (pyridostigmine bromide) is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

**CONTRAINDICATIONS**—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

**WARNINGS**—Use with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

*Usage in Pregnancy*—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—Side effects are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—Prior or simultaneous administration of atropine sulfate (0.6 to 1.2 mg; I.V.) is recommended to minimize the side effects (excessive secretions, bradycardia). Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether.

**CAUTION**—Federal law prohibits dispensing without a prescription.

**HOW SUPPLIED**—Regonol is available in: 2 ml ampuls—5 mg/ml boxes of 10. NDC #0052-0460-10

Organon

A PART OF Akzona INC.

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# WITH PHARMASEAL, YOU'RE ALWAYS WELL-CONNECTED.

When it comes to sterile, pressure monitoring/injection tubing, plastic stopcocks, and I.V. extension tubing, Pharmaseal makes sure you're well-connected.

First, for the best connections, our pressure monitoring/injection tubing is clearly better.

For one, both tubing and connectors are totally transparent for superb visibility. Plus, special winged connectors assure a secure fit.

Tubing is available with either male/female or male/male adapters in lengths from 6" to 84".

All tubes are also individually sealed in a sterile, peel-open package.

Most important of all, you can count on the tubing's total dependability for pressures up to 35 KG/CM² (500 psi).

Plus, we offer more stopcocks for more applications to meet more of your needs in the hospital.

One-way stopcocks.
Three-way stopcocks.
Four-way stopcocks.
Novex three-way stopcocks (for I.V. and other low pressure uses).

Stopcocks with special caps to protect ports, rotating Luer-lock adapters, pre-attached extension tubes and a wide variety of extension tubes.

All with smooth-turning handles and tight-fitting parts that won't stick or leak in normal use. (Approved for use up to 125 psi.)

And, we also offer custom monitoring kits including pressure tubing, stopcocks and disposable transducer domes.

Let us help you make the best connections in stopcocks, tubing and custom kits. For details and samples, just contact your Pharmaseal representative.

We want you to be well-connected.

**PHARMASEAL®**

© Pharmaseal
Glendale, CA 91201

ISSN 0003-2999
vol. 59, no. 6 June 1980

Acc.
3.11.8

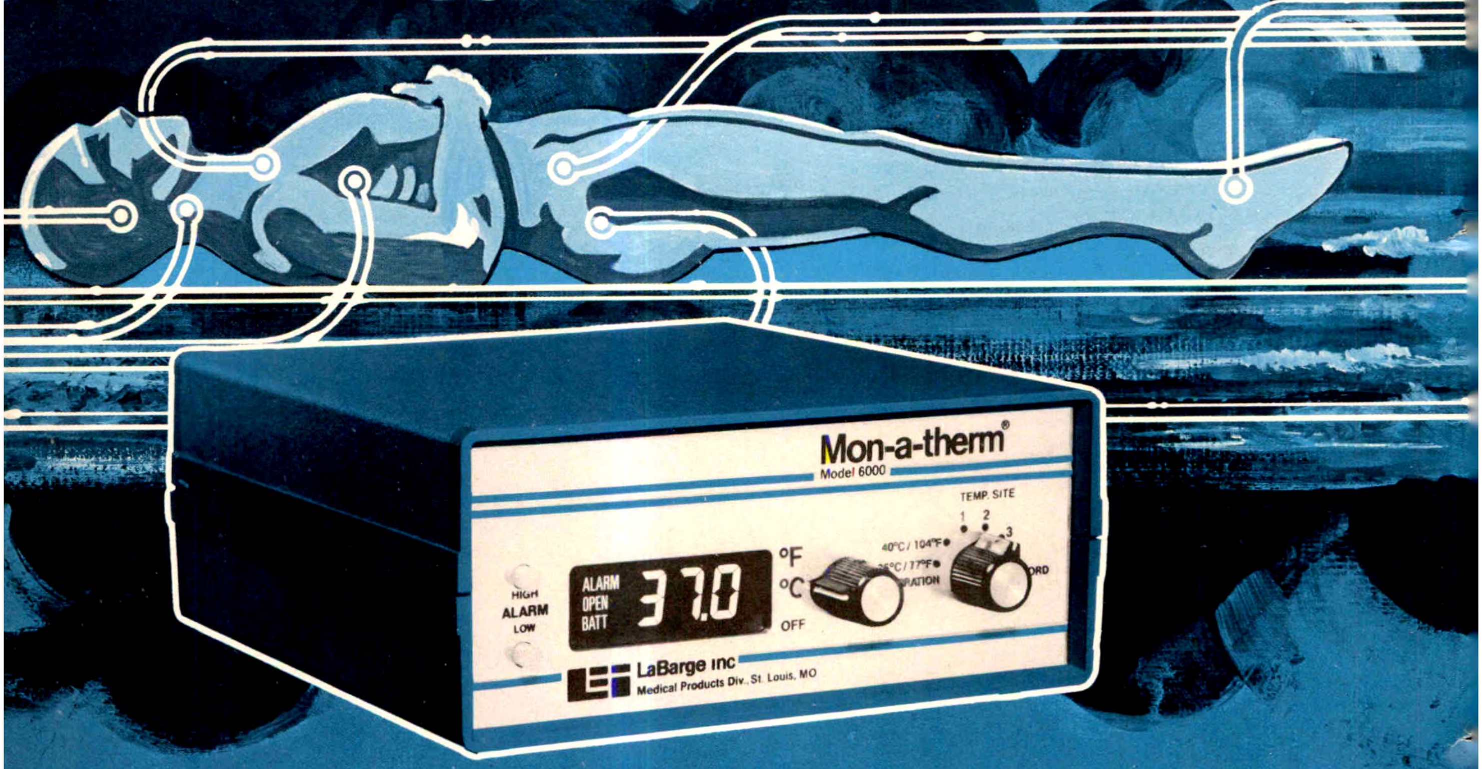
# Anesthesia and Analgesia

**Journal of the International Anesthesia Research Society**

OLDEST PUBLICATION IN THE SPECIALTY –
ESTABLISHED 1922

# A BREAK-THROUGH

## IN TEMPERATURE MONITORING DURING SURGERY



**Innovative features of the new Mon-a-therm® Model 6000 System:**

☐ Temp sites: multiple – monitor 3 sites simultaneously.

☐ Range: extended – for hyperthermia and hypothermia.

☐ Display: digital – °C or °F; backlighted LCD.

☐ Alarm: audio/visual – adjustable high-low limits.

☐ Calibration: confirmation – high-low calibration checks.

☐ Indicators: visual – alarm; open circuit; low battery.

Mon-a-therm® disposable temperature sensors:

■ skin ■ esophageal
■ rectal ■ tympanic
■ esophageal stethoscope with sensor
■ foley catheter with sensor
■ nasopharyngeal

**LaBarge Inc.**
**Medical Products Division**
**520 S. Jefferson Avenue**
**St. Louis, Missouri 63103**

**314 231-3400 in Missouri**
**800 325-3363 Toll Free**

Acc.
3.11.8

# Anesthesia and Analgesia

Journal of the
International Anesthesia Research Society

3645 Warrensville Center Road
Cleveland, Ohio 44122
Telephones (216) 295-1124, 295-1130

**EDITORIAL BOARD**

**Editor in Chief:**
**Nicholas M. Greene, M.D.,** New Haven, Connecticut

**Editors:**
**Henrik H. Bendixen, M.D.,** New York, New York
**D. Ryan Cook, M.D.,** Pittsburgh, Pennsylvania
**Benjamin G. Covino, Ph.D., M.D.,** Boston, Massachusetts
**Douglas B. Craig, M.D.,** Winnipeg, Manitoba, Canada
**E. Paul Didier, M.D.,** Rochester, Minnesota
**Norig Ellison, M.D.,** Philadelphia, Pennsylvania
**Alison B. Froese, M.D.,** Toronto, Ontario, Canada
**Daniel M. Philbin, M.D.,** Boston, Massachusetts
**Cedric Prys-Roberts, M.A., D.M., Ph.D.,** Bristol, United Kingdom
**N. Ty Smith, M.D.,** San Diego, California
**Robert K. Stoelting, M.D.,** Indianapolis, Indiana
**K. C. Wong, M.D., Ph.D.,** Salt Lake City, Utah

**Book Review Editor:**
**E. Paul Didier, M.D.,** Rochester, Minnesota

**ANESTHESIA AND ANALGESIA** (ISSN 0003-2999) is published monthly by the International Anesthesia Research Society, a non-profit scientific and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, M.D., Bruce F. Cullen, M.D., E. Paul Didier, M.D., Kenneth K. Keown, M.D., John T. Martin, M.D., Emerson A. Moffitt, M.D., Dean H. Morrow, M.D., B. B. Sankey, M.D., and Robert K. Stoelting, M.D. Emeritus Trustees are: Paul R. Dumke, M.D., Morris T. Nicholson, M.D., and T. H. Seldon, M.D.

**EDITORIAL CORRESPONDENCE** and manuscripts should be addressed to: **Nicholas M. Greene, M.D., Editor in Chief, Anesthesia and Analgesia, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: [203] 436-2887).** For information concerning preparation of manuscripts see "A Guide for Authors" published in each issue. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or in part is not permitted except by written consent of the publisher and the author.

**BOOKS FOR REVIEW** should be sent directly to the Book Review Editor, **E. Paul Didier, M.D., % Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55901.**

**REPRINTS:** For single copies, write directly to senior author at address listed on title page. Quantity orders (minimum 100) processed through Cleveland business office, prices on request.

**BUSINESS CORRESPONDENCE,** including subscription and membership payments, single issue purchases, change of address notices, and requests for membership applications, should be sent to: **B. B. Sankey, M.D., Executive Secretary and Business Manager, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122 (Telephones: [216] 295-1124, 295-1130).**

**SUBSCRIPTION RATES:** United States and U.S. possessions, $30.00 per year (12 issues); all other countries, $33.00.

**MEMBERSHIP DUES (Including Journal Subscription):** United States and U.S. possessions, $30.00 per year; all other countries, $33.00. **Membership** available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine or other disciplines who are engaged either in active clinical practice of or research in anesthesiology. **Associate Membership** available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). **Educational Membership** (half the full price) available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only, upon completion of application including certification by applicant's program director.

**SINGLE ISSUES:** $5.50 each beginning 1979; $4.50 for years 1970–1978; $3.00 for years 1954–1969; $2.00 for years 1928–1953. (See "Back Issues Available" or write to Cleveland business office for listing.)

**MAILING DATES:** Journals mailed 25th of month preceding issue date. Second class postage paid at Cleveland, Ohio and at additional mailing offices.

**CHANGE OF ADDRESS NOTICES:** Send to Cleveland business office as much in advance as possible to ensure correct addressing of Journals. Replacement copies of missing Journals will be furnished without charge only if original copy is returned by post office as undeliverable. POSTMASTER: Send address changes to Anesthesia and Analgesia, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

**ADVERTISING:** Rate sheets, including advertising clearance procedure, available from national advertising representative: Charles B. Slack, Inc., 6900 Grove Road, Thorofare, New Jersey 08086 (Telephone: [609] 848-1000). Orders, contracts, and classified ad copy should be sent to the Cleveland office. Reproduction materials and inserts should be sent to Waverly Press, Inc., 300 Idlewild Avenue, Easton, Maryland 21601.

© 1980, International Anesthesia Research Society.

LIBRARY

# Anesthesia and Analgesia

## EDITORIAL

**Prolonged Sensory/Motor Deficits following Inadvertent Spinal Anesthesia**—Covino BG, Marx GF, Finster M, and Zsigmond EK . . . . . 399

## SCIENTIFIC ARTICLES

**Deaths from Local Anesthetic-Induced Convulsions in Mice**—de Jong RH, and Bonin JD . . . . . 401

**Ketamine Suppression of Chemically Induced Convulsions in the Two-Day-Old White Leghorn Cockerel**—Reder BS, Trapp LD, and Troutman KC . . . . . 406

**Arrhythmogenic Effects of Aminophylline during Halothane Anesthesia in Experimental Animals**—Stirt JA, Berger JM, Ricker SM, and Sullivan SF . . . . . 410

**Reduction of Enflurane-Induced Spike Activity by Scopolamine**—Moorthy SS, Reddy RV, Paradise RR, Losasso AM, and Gibbs PS . . . . . 417

**Developmental Toxicity of Methoxyflurane in Mice**—Wharton RS, Sievenpiper TS, and Mazze RI . . . . . 421

**Effect of Halothane, Enflurane, and Nitrous Oxide on Tracheal Ciliary Activity in Vitro**—Lee KS, and Park SS . . . . . 426

**Glycopyrrolate-Neostigmine and Atropine-Neostigmine Mixtures Affect Postanesthetic Arousal Times Differently**—Baraka A, Yared J-P, Karam A-M, and Winnie A . . . . . 431

**Lidocaine or Thiopental for Rapid Control of Intracranial Hypertension?**—Bedford RF, Persing JA, Pobereskin L, and Butler A . . . . . 435

**Hemodynamic Effects of Diazepam and Diazepam-Nitrous Oxide in Patients with Coronary Artery Disease**—McCammon RL, Hilgenberg JC, and Stoelting RK 438

## CLINICAL REPORTS

**Acute Respiratory Distress as a Complication of Left Ventricular Cardiac Catheterization**—Cozanitis DA, and Heinonen J . . . . . 442

**Succinylcholine-Induced Hyperkalemia in a Patient with Parkinson's Disease**—Gravlee GP . . . . . 444

**Prolonged Neural Blockade following Regional Analgesia with 2-Chloroprocaine**—Ravindran RS, Bond VK, Tasch MD, Gupta CD, and Luerssen TG . . . . . 447

**Persistent Neurologic Deficit and Adhesive Arachnoiditis following Intrathecal 2-Chloroprocaine Injection**—Reisner LS, Hochman BN, and Plumer MH . . . . . 452

# Contents

June 1980
Vol. 59/No. 6

**A Guide-Wire Technique for Replacement of Swan-Ganz Catheters**—Shoum S, Kahn RC, Carlon GC, and Howland WS . . . . . 455
**A New Head Strap**—Chander S . . . . . 457

## LETTERS TO THE EDITOR

**Atropine in Physostigmine Reversal of Diazepam**—Cuka DJ, and Edelman JD; Belkin J; reply by Garber JG, Ominsky AJ, and Orkin FK . . . . . 459
**Correction**—Winnie AP . . . . . 460

## BOOK REVIEWS

**Pain—Association for Research in Nervous and Mental Disease, Volume 58**—Bonica JJ (Ed) . . . . . 461
**Hemotherapy in Trauma & Surgery**—The Committee on Workshops of the American Association of Blood Banks . . . . . 461
**Platelet Physiology & Transfusion**—The Committee on Workshops of the American Association of Blood Banks . . . . . 461
**Anesthesia & Neurosurgery**—Cottrell JE, and Turndorf H . . . . . 462
**Der Einfluss vol Anaesthetica auf die Kontraktionsdynamik des Herzens**—Fischer KJ . . . . . 462
**Zur Herzwirkung von Inhalationsanaesthetica**—Siepmann HP . . . . . 462
**The Control of Chronic Pain, Current Topics in Anaesthesia, Volume 2**—Lipton S 463
**Clinical and Resuscitative Data, Second Edition**—Dunnill RPH, Colvin MP, and Crawley BE . . . . . 463
**Key Words in Anesthesiology, Second Edition**—Greene NM . . . . . 463

YOU KNOW THE POSITIVE SIDE OF NARCOTIC-SUPPLEMENTED ANESTHESIA...

TITRATES THE RESPIRATORY DEPRESSION OUT

# NARCAN®

## naloxone HCl

## NEUTRALIZES THE NEGATIVE

### NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

### Useful when narcotic/$N_2O$ anesthesia is employed

### Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism

The duration of activity of some narcotics may exceed that of NARCAN®. Observe the patient closely and give repeat doses of NARCAN® if needed.

### Also available, NARCAN® NEONATAL naloxone HCl

Please see next page for complete prescribing information.

**Endo Laboratories, Inc.**
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, New York 11530

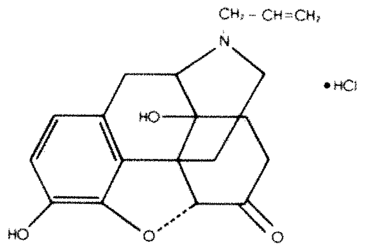
DU PONT
REG US PAT & TM OFF

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088.

## OF NARCOTIC-SUPPLEMEN[illegible]D ANESTHESIA

# NARCAN®
## naloxone HCl

**DESCRIPTION** NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

**ACTIONS** NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

**INDICATIONS** NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

**CONTRAINDICATIONS** NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

**WARNINGS** NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

**Usage in Pregnancy** Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

**PRECAUTIONS** In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

**ADVERSE REACTIONS** In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

**DOSAGE AND ADMINISTRATION** NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

**USAGE IN ADULTS Narcotic Overdose—Known or Suspected** The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

**Post Operative Narcotic Depression** For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

**USAGE IN CHILDREN Narcotic Overdose—Known or Suspected** The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

**USAGE IN NEONATES Narcotic-induced depression** The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

**HOW SUPPLIED** 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

**ANIMAL PHARMACOLOGY AND TOXICOLOGY** In the mouse and rat the intravenous $LD_{50}$ is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the $LD_{50}$ (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

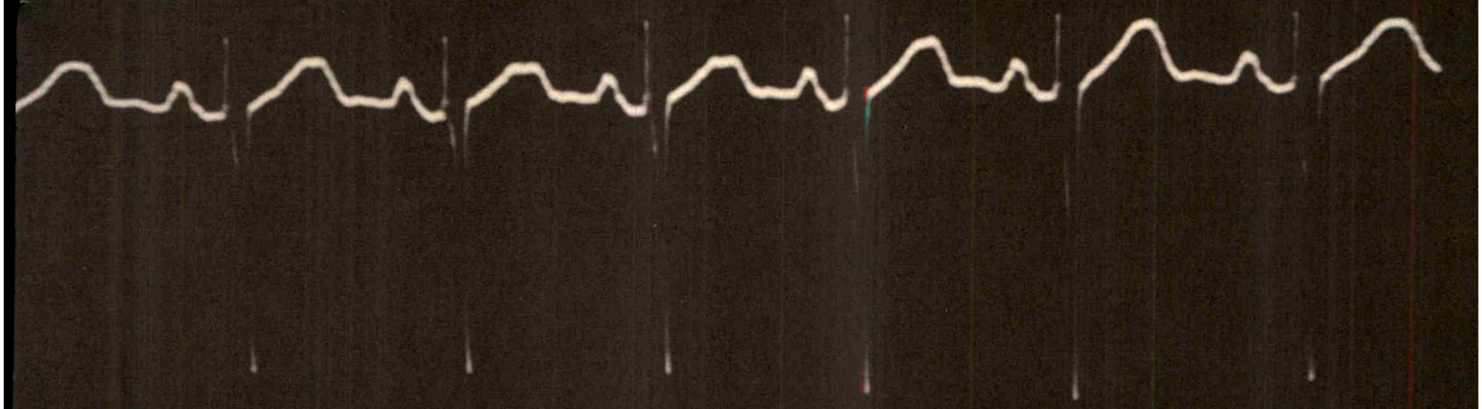
Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

**Endo Laboratories, Inc.**
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DU PONT
REG. U.S. PAT & TM OFF

EDO-050N

May, 1977



# The best trace... in the least time.

The trace shown here is what you can expect each time you monitor with NDM electrodes.

You will see a high amplitude signal with a narrow base line.

And you won't have to wait long for that remarkably narrow base line to stabilize. Monitoring can begin as soon as you have connected the leadwires.

Trace quality won't deteriorate during long procedures, or as a result of defibrillation, either. (Repeated 400 watt-second charges won't polarize NDM electrodes. A stable trace returns to your monitor within one second.)

With their ultra-low heating characteristics, NDM electrodes also reduce the chance of an electrosurgical mishap causing RF burns at ECG electrode sites.

There is an NDM electrode just right for your OR, including one with a special adhesive to resist contact loss from spilled fluids or prep solutions.

If you are making do with one of the thirty or so other electrode brands, please consider this: *Over half of the monitoring done in the U.S. is done with NDM electrodes.*

A trial will convince you, and it's yours for the asking. Returning the coupon can be the first step toward reducing your electrode problems.

Thank you

**NDM**® NEW DIMENSIONS IN MEDICINE
Distributed by American Hospital Supply

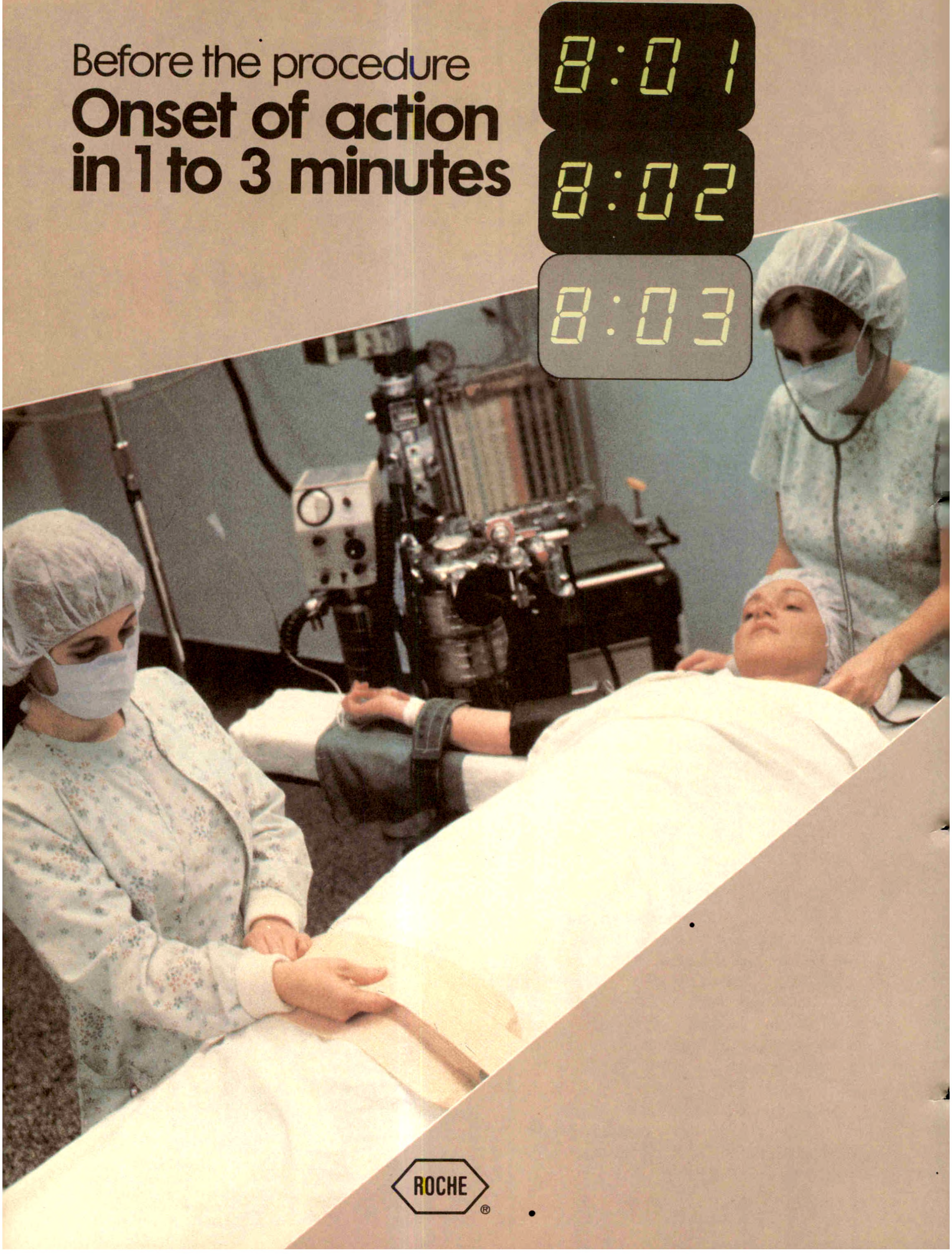
NDM Corporation, Dept. D
3040 E. River Road
Dayton, Ohio 45439

☐ Please have a representative contact me.
☐ Send information about NDM electrode systems.

Name: ____________ Title: ______
Hospital: ____________ Dept.: ______
Address: ____________
City: ______ State: ______ Zip: ______
Phone: ______ Ext.:

Before the procedure

# Onset of action in 1 to 3 minutes



ROCHE®

# After the procedure
# **Diminished recall**

## Preoperative relief with postoperative benefits

☐ Predictable course of action—onset within minutes, release within hours. As with most CNS-acting drugs, outpatients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, *e.g.*, operating machinery or driving.

☐ Calm relaxed patient, better prepared for the procedure.

☐ A proven record of safety and performance.

☐ Does not normally compromise cardiac or respiratory function. Resuscitative equipment should be readily available.

☐ Use with care in elderly, very ill and patients with limited pulmonary reserve (see Warnings section on following page).

☐ Narcotic dosage can and should be reduced.

**Injectable Valium® I.V.**
diazepam/Roche ⒸⅣ

A pattern of action
that meets your needs

Please see summary of product information on next page.

## New/Improved
# Tel-E-Ject®
## 10-mg Disposable Syringe (5 mg/ml)

scale on both sides of barrel eases visibility during administration

## Injectable
# Valium® I.V.
## diazepam/Roche

10-ml vials }
2-ml ampuls } 5 mg/ml

**Please consult complete product information, a summary of which follows:**

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:*** **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

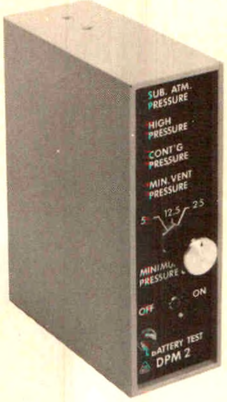
**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE®
ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

# NEW from NORTH AMERICAN DRÄGER

North American Drager is continually keeping in touch with the growing needs of the anesthesia profession. We are constantly improving our products for patient safety, our prime engineering and design criterion. These new products join the ever growing range of North American Drager Products of Anesthesia.



**DPM 2**
**(DRAGER PRESSURE MONITOR II)**

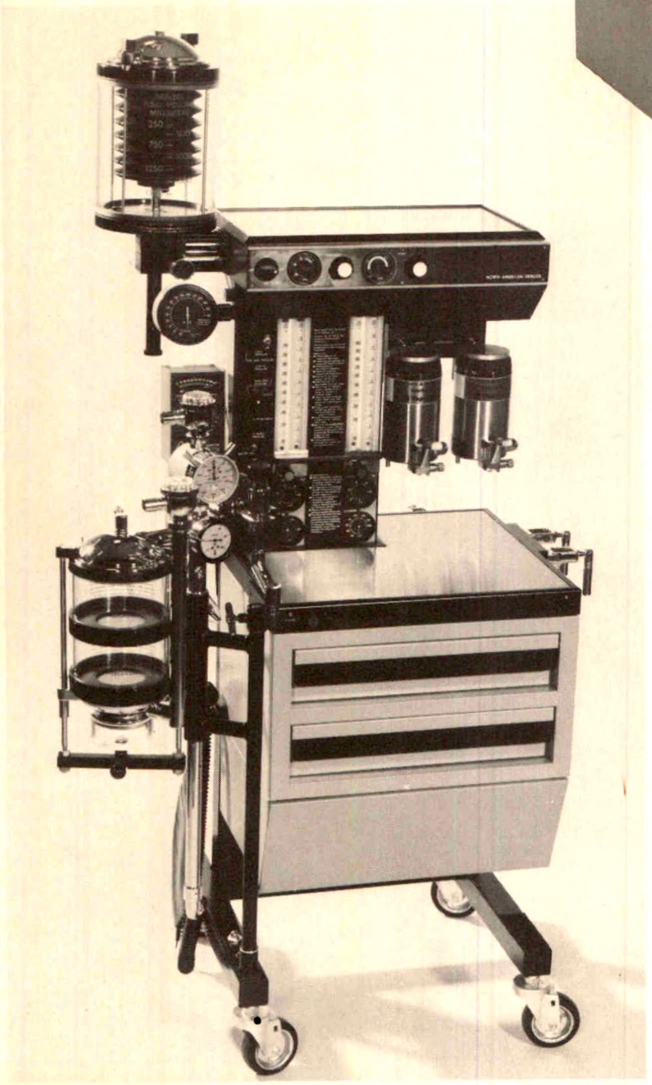
Our second generation of pressure monitors.
Four pressure monitors—minimum ventilation pressure, continuing pressure, high pressure and sub atmosphere pressure.

**VAPORIZER EXCLUSION SYSTEM**

A unique lock out system for insuring that only one vaporizer can be switched on at a time.

**PHILLIPS LARYNGOSCOPE BLADE**

Combines the features of the Miller Blade and the Jackson-Eversole Blade. Now in Two Sizes—Adult and Pediatric.



**NARKOMED 2 ANESTHESIA SYSTEM**

The newest member of the North American Drager family of Anesthesia Systems.
A complete anesthesia system consisting of an anesthesia dispensing system, ventilation system, patient monitoring system and a unique patient safety alarm system.

**NORTH AMERICAN DRÄGER**
148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969

**NORTH AMERICAN DRÄGER**
148B QUARRY ROAD • TELFORD, PENNSYLVANIA 18969

☐ Please send Anesthesia Accessories catalog

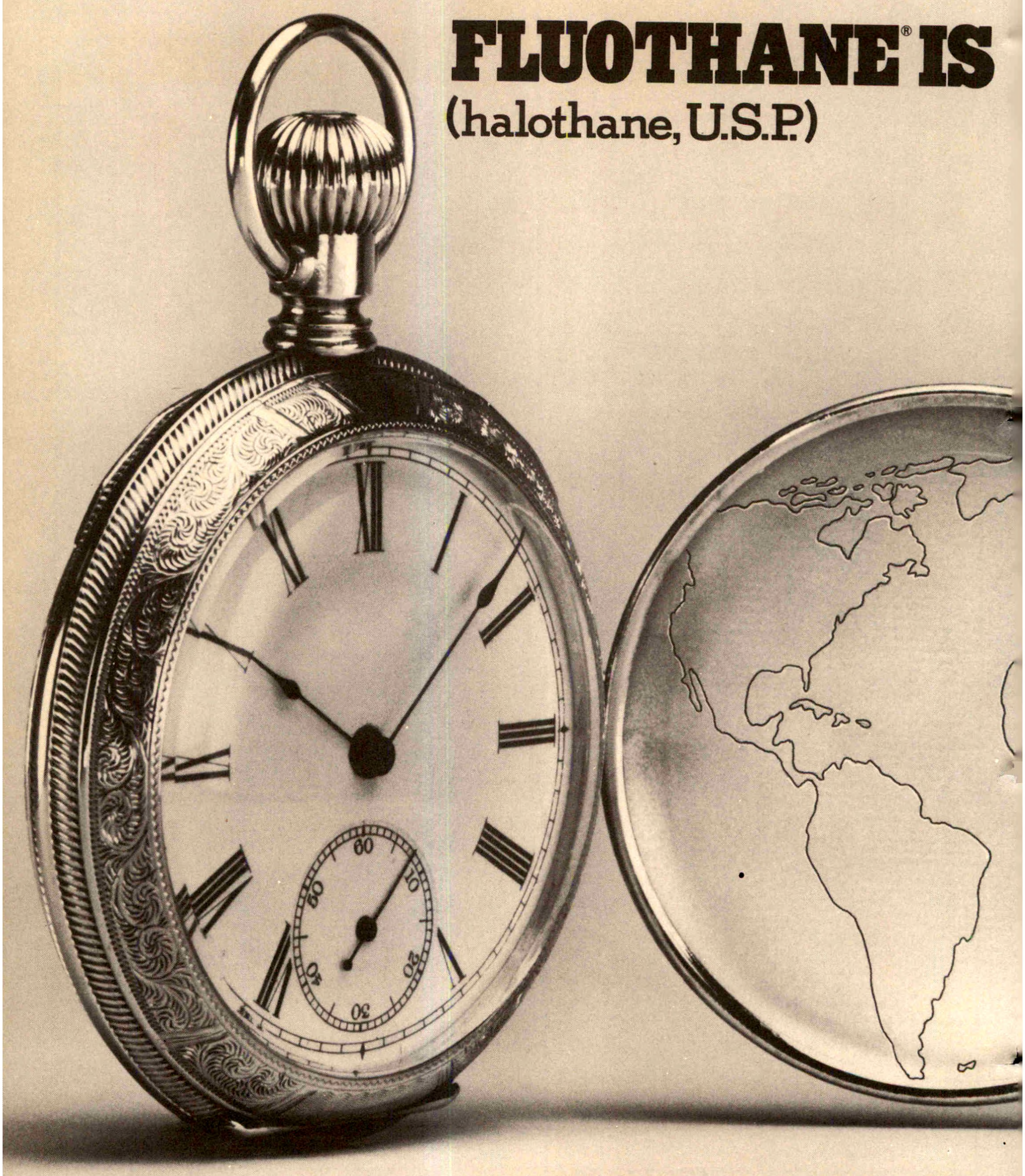
☐ Please have N.A.D. representative call

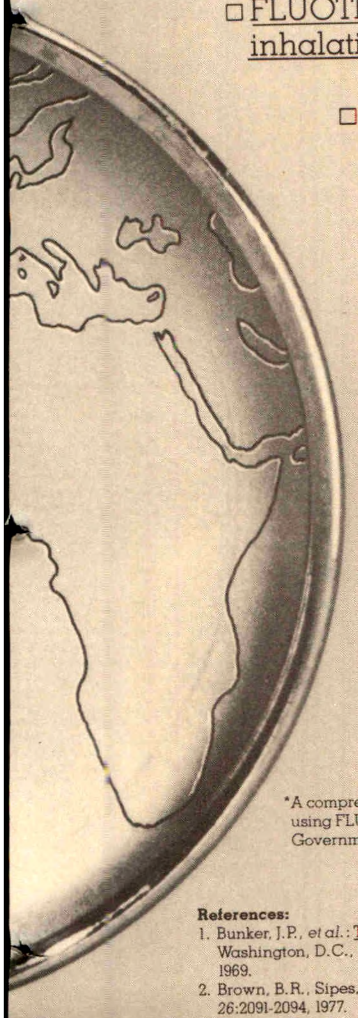
☐ Please include information on Anesthesia Machines

NAME ____________________
DEPARTMENT ____________________
HOSPITAL ____________________
ADDRESS ____________________
CITY ____________ STATE ______ ZIP ______
TELEPHONE ____________________

# EVERY TWO SECONDS FLUOTHANE® IS

(halothane, U.S.P.)





# THE WORLDWIDE CHOICE.

## Over 500 million administrations throughout the world. Well over 125 million administrations in the United States alone.

Somewhere in the world—every two seconds—someone makes another decision to use FLUOTHANE® (halothane, U.S.P.). And for good reasons:

☐ FLUOTHANE has been more widely investigated than any other inhalation anesthetic.

☐ The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and... the overall safety record of the anesthetic was excellent."[2]

☐ FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]

☐ FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.

☐ And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

**References:**

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. *26*:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology *43*:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

**Ayerst**® Ayerst Laboratories
New York, N.Y. 10017

## the most widely used inhalation anesthetic in the world

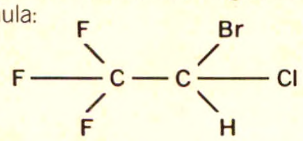
# FLUOTHANE®

## (halothane, U.S.P.)

## for a wide variety of techniques and procedures in patients of all ages

*(Complete text of package circular.)*

**Description.** FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

**Actions.** FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

**Indications.** FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

**Contraindications.** FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

**Warnings.** When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

*Usage in Pregnancy.* Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

**Precautions.** The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

**Adverse Reactions.** The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

**Dosage and Administration.** FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

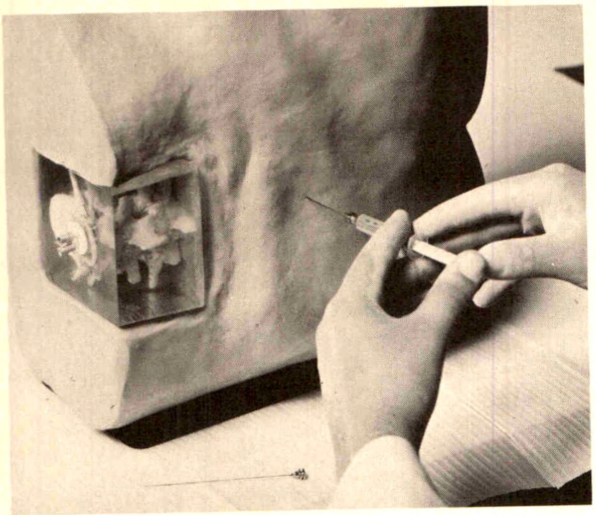
FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

**How Supplied.** No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P. stabilized with 0.01% thymol (w/w).

Ayerst® Ayerst Laboratories
New York, N.Y. 10017

7197/80

**Tap our resources**



Provide practical learning experience in your training sessions with realistic Life/form® products from Nasco. The **free** Health Care Educational Materials Catalog describes exceptional selection of anatomical replicas and simulators. Molded from actual organs in lifelike vinyl, they offer both visual and tactile learning experiences.

The spinal injector simulator, for example, features a clear plastic window at the top of the model. It displays the L1 and L2 sections of the vertebral column, as well as other anatomical details. With the functional portion, students get the "actual feeling" for performing all types of spinal injections.

Catalog includes many other simulation devices, models, charts and visual media for all areas of medical education. Send for your free copy today. Write Dept. RA-804.

**Free Phone Order Service 1-800-558-9595**
**In Wisconsin 1-800-242-9587**

Nasco

Fort Atkinson, WI 53538  Modesto, CA 95352

## *I.A.R.S. 1980*
## REVIEW COURSE LECTURES
## AND
## ABSTRACTS OF SCIENTIFIC PAPERS

200-page booklet including 16 Review Course Lectures and Abstracts of 62 scientific papers given at the IARS 54th Congress, March 10–13, 1980. Copies available now from IARS Cleveland office - $5.00 per copy.

I.A.R.S.
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Enclosed is check for $______ for ______ copy(ies) of "1980 Review Course Lectures" to be sent to:

(name)

(Mail address)

(City-state-zip)

# *Anesthesia and Analgesia*

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | 4 | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | 4 | 5 | 6 |
| 36 | 1957 | – | 2 | – | – | – | 6 | 44 | 1965 | – | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | 3 | 4 | 5 | 6 |
| 38 | 1959 | – | 2 | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | 5 | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | 2 | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | 3 | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | 4 | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | – | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | 3 | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 |
| 59 | 1980 | 1 | | | | | |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.
BOUND VOLUMES AVAILABLE: $8.00—For Years 1947, 1948, 1949; $10.00—For Years 1953, 1955
OTHER PUBLICATIONS AVAILABLE:

"Basic and Clinical Physiology of the Liver" (Supplement to Sept.-Oct. 1965 issue)—$3.00.
Ten-Year (1960-1969) Cumulative Index—$3.00.
Ten-Year (1970-1979) Cumulative Index—$3.00.
1979 (53rd Congress) Review Course Lectures—$5.00.
1980 (54th Congress) Review Course Lectures & Abstracts—$5.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122
Please send me the publications circled above, or listed hereunder:

☐ Check for $_____ enclosed.
☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name ____________________

Address ____________________

City, State, Zip ____________________

# Emotional and Psychological Responses to Anesthesia and Surgery

Edited by FRANK GUERRA, M.D. and J. ANTONIO ALDRETE, M.D.

CONTENTS: *F. Guerra*, Awareness Under General Anesthesia. *H. J. Schlesinger et al.*, Effects of Psychological Intervention on Recovery from Surgery. *C. J. Getto*, Preoperative Depression. *M. P. Weissberg*, Suicide and Surgery. *J. L. Fleming*, Nonpharmacological Methods for Dealing with Preoperative Anxiety: The Uses of Supportive Conversation. *T. L. Thompson II*, Psychological Aspects of Open Heart Surgery. *J. A. Boswick, Jr.*, Psychological Considerations in Burn Patients. *I. Penn and S. L. Dubovsky*, Psychiatric Considerations in Transplant Surgery. *J. A. Aldrete*, Psychological and Ethical Issues in Anesthesia for Transplant Surgery. *F. Guerra and L. Usubiaga*, Anesthetizing the Patient on Psychoactive Medication. *P. Wexler*, Psychological Mangement of the Parturient and the Neonate. *C. H. Lockhart*, Practical Considerations in the Preoperative Psychological Preparation of the Pediatric Patient. *D. J. Steward*, Psychological Considerations in the Pediatric Patient. *H. P. Coppolillo*, Management of the Child in the Perioperative Period. *J. G. Modell and F. Guerra*, Psychological Problems in the Surgical Patient. *L. Miller*, Psychological Assessment of the Intensive Care Patient. *L. Miller and G. R. Haun*, Stress and the Intensive Care Nurse. *R. L. Steig*, Chronic Pain. *K. M. Wood*, The Chronic Pain Patient—A Personal Perspective. *F. Guerra*, Death and the Anesthesiologist. *V. M. T. Garner*, Specific Ethno-Cultural Considerations in the Perioperative Period. Index.

*1980, 266 pp., $23.50 ISBN: 0-8089-1195-3*

# Cardiac Anesthesia

Edited by JOEL A. KAPLAN, M.D.

"Many cardiac anesthetists will find after reading this book that their standards of monitoring and care do not begin to approach the excellence of the Emory program. This book will set a standard of good practice for all of us to strive toward. . . . The book is a good, complete coverage of the topic and the Emory group is to be congratulated for the quality of their writing. The book is well referenced with clear illustrations."—J. Kent Garman, M.D., ANESTHESIA AND ANALGESIA

CONTENTS: *J. W. Hurst et al.*, Foreword. PHARMACOLOGY AND MONITORING. *C. C. Hug, Jr.*, Pharmacology—Anesthetic Drugs. *C. C. Hug, Jr. and J. A. Kaplan*, Pharmacology—Cardiac Drugs. *J. A. Kaplan*, Hemodynamic Monitoring. *J. A. Kaplan*, Electrocardiographic Monitoring. DISEASE ENTITIES AND ANESTHESIA. *L. M. Abrams and D. A. Chambers*, Preoperative Management of the Cardiac Surgical Patient. *D. A. Chambers*, Anesthesia for the Patient with Acquired Valvular Heart Disease. *J. L. Waller et al.*, Anesthesia for Coronary Revascularization. *J. W. Bland and W. H. Williams*, Anesthesia for Treatment of Congenital Heart Defects. *J. R. Zaidan*, Pacemakers. *R. W. Dunbar*, Thoracic Aneurysms. *J. A. Kaplan and R. W. Dunbar*, Anesthesia for Noncardiac Surgery in Patients with Cardiac Disease. SUPPORT OF THE CIRCULATION. *D. C. Finlayson and J. A. Kaplan*, Cardiopulmonary Bypass. *J. A. Kaplan and J. M. Craver*, Assisted Circulation. POSTOPERATIVE CARE OF THE PATIENT. *D. C. Finlayson*, Postoperative Intensive Care. *J. A. Kaplan*, Pericardial Diseases. *J. T. Bonner*, Cardiopulmonary Resuscitation. Index.

*1979, 544 pp., Illus., $44.75 ISBN: 0-8089-1125-2*

**GRUNE & STRATTON**

*A Subsidiary of Harcourt Brace Jovanovich, Publishers*

111 FIFTH AVENUE, NEW YORK, N.Y. 10003
24-28 OVAL ROAD, LONDON NW1 7DX

Please send me the following:

___copies, *Guerra*: Emotional and Psychological Responses to Anesthesia and Surgery, *$23.50*

___copies, *Kaplan*: Cardiac Anesthesia, *$44.75*

Please check one box:

☐ Payment enclosed (*Free postage and handling. Add applicable sales tax*)
☐ Visa ☐ Master Charge* ☐ American Express
☐ Diner's Club

Charge Card No.______

Expiration Date: Month______Year______

*For Master Charge include the numbers that appear above your name______

Your Signature______

On prepaid orders, payment will be refunded for titles on which shipment is not possible within 120 days. Prices are in U.S. dollars and subject to change without notice.

NAME______
(please print)
AFFILIATION______
ADDRESS______
CITY/STATE/ZIP______

☐ Please check if you are a Grune & Stratton or Academic Press Author.

Direct all orders to Georgia Phillips, Media Dept.

*Anes Ana /6/80*

See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

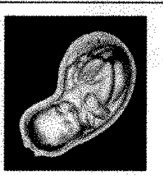
# More protection for the newborn.

# Marcaine® hydrochloride

brand of

# bupivacaine hydrochloride

with or without epinephrine 1:200,000



**Indications:** Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

**Contraindication:** Marcaine is contraindicated in patients with known hypersensitivity to it.

**Warnings:** RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

*Usage in Pregnancy.* Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

**Precautions:** The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

**Adverse Reactions:** Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

*Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

*Treatment of Reactions.* Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

**References:**

1. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.
2. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
3. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.

BREON

**BREON LABORATORIES INC.**
90 Park Avenue, New York, N.Y. 10016

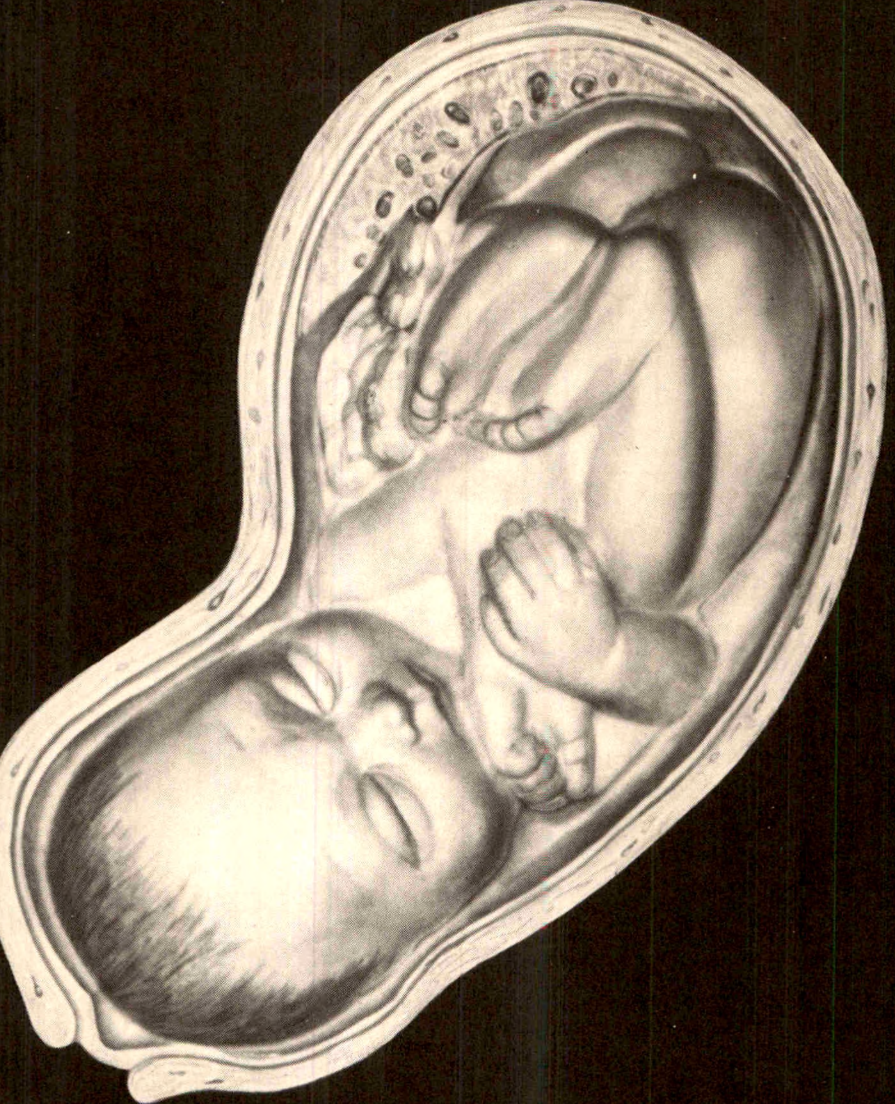
**FORMULA**

| PRODUCT IDENTIFICATION | | | MULTIPLE DOSE VIAL | | | | | | SINGLE DOSE AMPUL | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Marcaine HCl (brand of bupivacaine HCl) % | mg./ml. | Epinephrine* (as bitartrate) Dilution | Methylparaben mg./ml. | Sodium Bisulfite mg./ml. | Thioglycerol ml./ml. | Ascorbic Acid mg./ml. | 60% Sodium Lactate ml./ml. | Edetate Calcium Disodium mg./ml. | Sodium Bisulfite mg./ml. | Thioglycerol ml./ml. | Ascorbic Acid mg./ml. | 60% Sodium Lactate ml./ml. | Edetate Calcium Disodium mg./ml. |
| 0.25 | 2.5 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 0.25 | 2.5 | 1:200,000 | 1 | 0.5 | .001 | 2 | .0017 | 0.1 | .5 | .001 | 2 | .0017 | 0.1 |
| 0.5 | 5.0 | — | 1 | — | — | — | — | — | — | — | — | — | — |
| 0.5 | 5.0 | 1:200,000 | 1 | 0.5 | .001 | 2 | .0017 | 0.1 | .5 | .001 | 2 | .0017 | 0.1 |
| 0.75 | 7.5 | — | | | | | | | — | — | — | — | — |
| 0.75 | 7.5 | 1:200,000 | Not Available in Vials | | | | | | .5 | .001 | 2 | .0017 | 0.1 |

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved. Federal law prohibits dispensing without a prescription.

More protection
for the newborn



A drug of choice for epidural anesthesia that results in

- decreased placental transfer[1]
- fewer neurobehavioral changes than lidocaine or mepivacaine[2,3]

**Marcaine® hydrochloride**
brand of
**bupivacaine hydrochloride**
with or without epinephrine 1:200,000

See adjacent page for prescribing information. Not recommended for paracervical block.
Model © by Hubbard Scientific Co. Northbrook, Ill.

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

## 55th CONGRESS to be held MARCH 8-12, 1981

## PEACHTREE PLAZA HOTEL, ATLANTA, GEORGIA

**CALL FOR PAPERS**

AUGUST 22, 1980 DEADLINE

If you would like to submit a paper for consideration by the Program Committee, please note the deadline for submitting title and 300-word abstract is August 22, 1980.

For official application form, please write or call:

E. Paul Didier, M.D., Chairman
Program Committee for 55th Congress
c/o Department of Anesthesiology
Mayo Clinic
200 First Street, SW
Rochester, Minnesota 55901

Telephone: (507) 286-8766

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

SCIENTIFIC EXHIBITS: Requests for applications for scientific exhibit space should be sent to: B. B. Sankey, M.D., International Anesthesia Research Society, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. (Please note the above deadline does not apply to scientific space applications which can be accepted, on a space availability basis, up to December 31, 1980.)

**MARK YOUR CALENDAR NOW—PLAN TO ATTEND THIS IMPORTANT CONTINUING MEDICAL EDUCATION ACTIVITY**

# EDITORIAL

# Prolonged Sensory/Motor Deficits following Inadvertent Spinal Anesthesia

THE REPORTS in the present issue by Ravindran et al[1] and by Reisner et al[2] are representative of several cases that have recently occurred in which relatively large volumes of 2% or 3% chloroprocaine intended for extradural injection were inadvertently injected intrathecally with resulting "total" spinal anesthesia and, most important, severe sensory and motor deficits lasting as long as several weeks. A conference was organized by Pennwalt Pharmaceutical Division, Pennwalt Corporation, Rochester, NY, the manufacturer of chloroprocaine (Nesacaine), to review and discuss the possible etiology of this phenomenon. The consultants were unanimous in their opinion that injection of large volumes of chloroprocaine with its low pH (Table) has been the one common factor in all the cases. Since the buffering capacity of the cerebrospinal fluid is poor, the inadvertent injection of a large volume of an acid solution may have caused acidification of the CSF, which in turn resulted in prolonged sensory/motor deficits. Acidity of the local anesthetic solution (Table) may also have played a role in the reported prolonged muscular impairment following the use of lidocaine-epinephrine[3] or bupivacaine-epinephrine.[4] The possibility that the acid local anesthetic solution causes severe vasoconstriction in the subarachnoid space, leading to a "spinal artery"[5]-type syndrome, was considered, but no experimental evidence is available in this regard.

The administration of small volumes (1 to 3 ml) of chloroprocaine into the subarachnoid space of dogs and man has, to our knowledge, not been associated with any prolonged neurologic deficits. However, the conference recommended that additional animal studies should be conducted to determine the effect of acidic solutions injected into the subarachnoid space.

Recently, inadvertent intrathecal injection of full anesthetizing doses of chloroprocaine also occurred in two obstetric units within the greater New York Metropolitan area. In both instances, however CSF was promptly drained out of the catheter and neither patient had prolonged sequelae. The readiness of the anesthesiologists involved to remove CSF may be related to Louis Orkin's vivid description of how the late Raphael Robertazzi saved a grave situation. Informed that a potentially fatal dose of more than 1 g of procaine had been injected as a spinal anesthetic, he rapidly inserted a large bore needle into the patient's cisterna magna, had another needle placed in the lumbar area, and irrigated repeatedly with normal saline in a caudad direction. The patient made an uneventful recovery.

Based on the discussion at the conference, the following steps for prevention and treatment are recommended:

1. Careful testing to rule out inadvertent intrathecal (or intravascular) placement of the "extradural" catheter; the test-dose must be of adequate magnitude (e.g., 4 to 5 ml of 2% chloroprocaine or 3 ml of 3% chloroprocaine) and the time allotted before subse-

**TABLE**

**pH of Local Anesthetic Drugs as Determined in Anesthesiology Laboratory of Columbia University**

| Drug | pH |
|---|---|
| Bupivacaine 0.5% plain | 4.975 |
| Bupivacaine 0.5% with epinephrine | 3.781 |
| Chloroprocaine 2% CE | 3.167 |
| Chloroprocaine 3% CE | 3.126 |
| Lidocaine 1% plain | 6.137 |
| Lidocaine 1% with epinephrine | 3.869 |
| Lidocaine 2% plain | 6.128 |
| Lidocaine 2% with epinephrine | 4.057 |
| Prilocaine 2% plain | 6.378 |

---

Reprint requests to Dr. Covino.

quent injection must be of sufficient duration (3 to 4 minutes) to permit symptoms of spinal anesthesia (or CNS irritability) to develop. To facilitate recognition and report of subtle symptoms of intrathecal (or intravascular) injection, the patient should not be heavily sedated.

2. Injection of a large, single therapeutic dose through a catheter should be avoided; instead, repeated fractional doses are advocated.

3. Should an inadvertent dural puncture precede correct placement of the extradural catheter, local anesthetic solutions with a higher pH should be selected.

4. In case a full anesthetizing dose of a highly acid local anesthetic solution has been injected intrathecally, CSF should be withdrawn as soon as possible; it is best to remove most of the anesthetic solution. In any case, at least 10 ml should be aspirated. If the injected volume was very large, irrigation with physiologic saline (without preservative and without glucose) may be beneficial. However, for treatment to be effective, it must be undertaken within the first 15 to 20 minutes.

An unsigned editorial in *Anesthesiology* (11:253–254, 1950), devoted to the "growing pains of spinal anesthesia," concluded with a statement which is equally pertinent to the present situation: "In the final analysis, it is not the drug that is important, but what is done with it."

Benjamin G. Covino, PhD, MD
*Harvard Medical School*
*Affiliated Hospitals Center*
*Boston, Massachusetts 02115*
Gertie F. Marx, MD
*Albert Einstein College of Medicine*
*Bronx, New York 10461*
Mieczyslaw Finster, MD
*Columbia College of Physicians*
*and Surgeons*
*New York, New York 10032*
Elmer K. Zsigmond, MD
*University of Illinois*
*Chicago, Illinois 60612*

## REFERENCES

1. Ravindran R, Bond VK, Tasch MD, et al: Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 59:447–451, 1980
2. Reisner LS, Hochman BN, Plumer MH: Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 59:452–454, 1980
3. Craig DB, Habib GG: Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. Anesth Analg 56:219–221, 1977
4. Cuerden C, Buley R, Downing JW: Delayed recovery after epidural block in labour. Anaesthesia 32:773–776, 1977

ANESTH ANALG
59:401-405, 1980

# Deaths from Local Anesthetic-Induced Convulsions in Mice

**Rudolph H. de Jong, MD,* and John D. Bonin, MA†**

---

DE JONG, R. H., AND BONIN, J. D.: Deaths from local anesthetic-induced convulsions in mice. Anesth Analg 59: 401–405, 1980.

Median convulsant ($CD_{50}$) and median lethal ($LD_{50}$) doses of three representative local anesthetics were determined in adult mice to evaluate the threat to life of local anesthetic-induced convulsions. The $CD_{50}$ and $LD_{50}$, respectively, were 57.7 and 58.7 mg/kg for bupivacaine, 111.0 and 133.1 mg/kg for lidocaine, and 243.4 and 266.5 mg/kg for chloroprocaine. When given intraperitoneally, bupivacaine thus was only about twice as toxic as lidocaine and four times as toxic as chloroprocaine. Convulsions always preceded death, except after precipitous cardiopulmonary arrest from extreme doses. A $CD_{50}$ dose of local anesthetic (causing convulsions in 50% of mice) was fatal in 90% of bupivacaine-induced seizures, in 57% of the chloroprocaine group, and in 6% of the lidocaine group. The narrow gap between convulsant and lethal doses of local anesthetics indicates that untreated convulsions present much more of a threat to life than heretofore appreciated.

**Key Words:** ANESTHETICS, Local: lidocaine; ANESTHETICS, Local: bupivacaine; ANESTHETICS, Local: chloroprocaine; TOXICITY: local anesthetic.

---

WHEN comparing the toxicity of drugs with similar action, the median lethal dose ($LD_{50}$) is the usual yardstick. Counting the number of animals that die within a preselected number of hours is straightforward, and the $LD_{50}$ derived therefrom provides a ready guide to setting upper limits for the drug's use in man. Adherence to these bounds has made death attributable to local anesthetic overdosage a rare event.

Nevertheless, toxic reactions to local anesthetics still occur when used in the upper dose ranges. One of the most severe of these systemic toxic responses is a generalized convulsion. Although immediate treatment usually leads to full recovery, convulsions are by no means harmless, and the threat of potential disaster is always there. How great is that threat?

Lacking a homogeneous and consistent data base for interagent comparisons, we evaluated the threat to life from local anesthetic-induced convulsions, and compared the lethality of convulsions induced by three commonly used local anesthetics. We used healthy adult white mice of the same strain, age, and sex; bracketed the median with four or five doses in groups of 10 mice each; and processed the data with a logistic curve-fitting technique that avoids end-value approximations.

We found a surprisingly narrow gap between the median convulsant and median lethal doses of these three local anesthetics: i.e., untreated convulsions present much more of a threat to life than is commonly recognized. We also found the toxicity of bupivacaine (relative to lidocaine) to be considerably less than heretofore estimated in mice.

## Methods

Adult (8 to 10 weeks old) outbred virgin female white Charles River mice were housed five to a cage, and away from males, to suppress estrus.[1] Ten mice at a time, each weighing approximately 30 g, were given a local anesthetic solution intraperitoneally and

---

* Richard Saltonstall Professor for Research in Anesthesia.

† Research Assistant.

Supported by Biomedical Research Support Grant #27913-0 of Tufts University School of Medicine, and by a grant from the American Society of Regional Anesthesia.

Received from the Anesthesia Research Laboratories, Tufts University School of Medicine, 136 Harrison Ave., Boston, Massachusetts 02111. Accepted for publication February 4, 1980.

Reprint requests to Dr. de Jong.

then placed in warmed cages for individual observation; animals were used once only. The 218 mice were given injections between 9 and 11 a.m. to minimize circadian variations in the convulsant threshold.[2] We recorded time of onset of ataxia, aimless running motions, arching of tail and neck, convulsions (graded +, ++, or +++ according to severity), color of skin and mucous membranes, respiratory distress, and time of recovery or death.

We chose a short-acting amide anesthetic (lidocaine), a long-acting amide agent (bupivacaine), and a brief-acting representative of the ester-class of drugs (chloroprocaine). Local anesthetics were donated by the respective manufacturer, supplied in sterile vials as the hydrochloride salt dissolved in saline. In keeping with the logarithmic nature of the dose-response curve, doses (in mg/kg) were increased or decreased in geometric proportion so as to bracket the median value with four or five points for each drug. Noncontributing duplicate end-values of 0% or 100% responses were discarded.

Observations on 139 mice fitting the above criteria were analyzed with an iterative curve-fitting technique that fits data points individually to a logistic curve, rather than as members of a collective group—thereby avoiding the pitfalls of transforming and weighting, and of approximating end-values at the 0% or 100% level.[3,4] The median convulsant dose (CD$_{50}$) and median lethal dose (LD$_{50}$) plus their standard errors were computed separately, as were the corresponding logit-transformed dose-response equations. (Recall that the median dose of a drug causes 50% of subjects to respond, and 50% not to respond.)

## Results

Soon after injection the animal's righting reflex began to fade, so that the animal attempted to right herself with rapid running motions of the extremities. We distinguished these righting motions from convulsions by the following criteria: running motions are alternating continuous movements, whereas convulsions are spasmodic synchronous contractions of the extremities; a "running" mouse is limp, whereas a convulsing mouse is stiff; tonic arching of the tail, back and neck always precedes convulsions. Convulsions were graded on a three-point scale, where + referred to a few mild jerks, ++ to repeated convulsions alternating with quiet interictal intervals, and +++ to status epilepticus.

Convulsions, when they occurred, rapidly ensued following intraperitoneal injection—usually within 1 minute (range ½ to 1½), with a trend toward earlier start with higher doses. With the amide anesthetics, when seizures proved fatal they lasted 1 to 1½ minutes before death supervened. At lower doses, convulsions in mice who recovered were brief, some mice had only one or two seizures. Nonfatal convulsions from chloroprocaine or bupivacaine generally lasted 1 to 3 minutes; those from lidocaine lasted considerably longer (5 to 7 minutes). Unless cardiorespiratory arrest from massive drug doses ended life within the first minute, convulsions always preceded death. Convulsing animals had rapid shallow respirations between convulsions; when about to recover, breathing slowed and tidal volume increased. In dying animals, on the other hand, breathing became progressively more shallow, pallor and cyanosis appeared, convulsions ceased, and the animal became limp and then died.

Raw data for the three local anesthetics are listed in Table 1. Table 2 shows the computed median convulsant doses (CD$_{50}$) and median lethal doses (LD$_{50}$)

**TABLE 1**
**Experimental Observations**

| | Sample size | Convulsions | Deaths |
|---|---|---|---|
| Bupivacaine (mg/kg) | | | |
| 50.4 | 10 | 2 | 1 |
| 56.5 | 10 | 5 | 5 |
| 63.5 | 11 | 8 | 7 |
| 80.0 | 10 | 9 | 10 |
| Lidocaine (mg/kg) | | | |
| 75.6 | 9 | 1 | 0* |
| 95.3 | 9 | 2 | 0 |
| 120.0 | 10 | 6 | 1 |
| 134.7 | 10 | 8 | 6 |
| 151.2 | 10 | 9 | 9 |
| Chloroprocaine (mg/kg) | | | |
| 200.0 | 10 | 2 | 0 |
| 224.5 | 10 | 4 | 2 |
| 252.0 | 10 | 6 | 4 |
| 317.5 | 10 | 8 | 8 |
| 400.0 | 10 | 1† | 10 |

* Duplicate end-value; not used in computation.
† Nine of 10 mice died without first convulsing.

**TABLE 2**
**Median Response Values**

| | CD$_{50}$* | LD$_{50}$† |
|---|---|---|
| | *mg/kg* | |
| Bupivacaine | 57.7 ± 2.7 | 58.7 ± 2.0 |
| Lidocaine | 111.0 ± 6.3 | 133.1 ± 3.3 |
| Chloroprocaine | 243.4 ± 14.5 | 266.5 ± 11.6 |

* Median convulsant dose and standard error.
† Median lethal dose and standard error.

and standard errors. Noteworthy is the narrow gap between convulsant and lethal dose. Figs. 1 and 2 provide linearized log dose-response curves to illustrate the relation between the incidence of convulsions and deaths, respectively, and the local anesthetic dose.

The computations in Table 3 detail the association between $LD_{50}$ and $CD_{50}$. The first column quantitates the proximity of convulsant dose to lethal dose; for bupivacaine, the values differ by less than 2%. Even with lidocaine there is only a 20% margin between convulsant and lethal dose, whereas with chloroprocaine a margin of only 10% lies between these two extremes. The second column of Table 3 derives the expected lethality of a convulsant dose by interpolating the $CD_{50}$ value in the dose-mortality equation. Thus 57.5 mg/kg of bupivacaine, which induces convulsions in 50% of mice, is lethal to 45% of mice. Since, at that dose level, convulsions always precede death, nine of 10 mice with bupivacaine-induced convulsions will die if left untreated. On the other hand, 111.0 mg/kg of lidocaine, which induces convulsions in 50% of mice, is lethal to 2.9% overall, so that fewer than 6% of mice convulsing from lidocaine will die. In other words, chances of surviving an untreated lidocaine-induced convulsion are about 16 out of 17, as against about 2 in 5 with chloroprocaine-induced convulsions, and 1 in 10 with bupivacaine-induced convulsions.

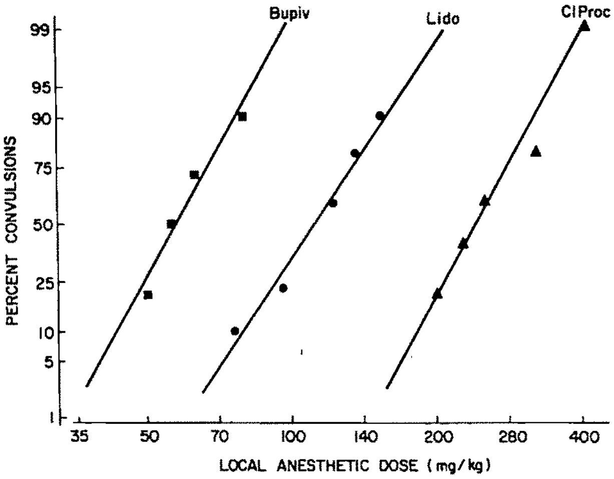


FIG 1. Dose response curves for bupivacaine (Bupiv), lidocaine (Lido), and chloroprocaine (ClProc). Drug dose, expressed in milligrams per kilogram, is on the logarithmic horizontal axis. The vertical axis represents percentage of convulsions on a probit-transformed response scale.

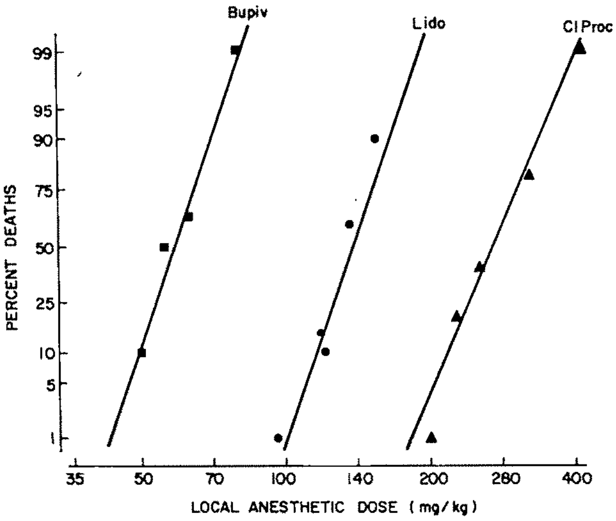


FIG 2. Dose-response curves for bupivacaine (Bupiv), lidocaine (Lido), and chloroprocaine (ClProc). Drug dose, expressed in milligrams per kilogram, is on the logarithmic horizontal axis. The vertical axis represents percentage of deaths on a probit-transformed response scale.

**TABLE 3**

**Lethal versus Convulsant Doses**

| | $LD_{50}/CD_{50}$ | Lethality of $CD_{50}$* |
|---|---|---|
| | % | |
| Bupivacaine | 101.7 | 90.2 |
| Lidocaine | 119.9 | 5.8 |
| Chloroprocaine | 109.5 | 57.0 |

* Percentage deaths attributable to a $CD_{50}$ dose, computed by interpolating the $CD_{50}$ value into the log dose-mortality equation.

**TABLE 4**

**Comparative Toxicity (Mass Ratios)**

| | Convulsions | Deaths |
|---|---|---|
| Lidocaine/Bupivacaine | 1.92 | 2.27 |
| Chloroprocaine/Lidocaine | 2.19 | 2.00 |
| Chloroprocaine/Bupivacaine | 4.21 | 4.54 |

The median dose ratios between pairs of local anesthetics tabulated in Table 4 confirm that bupivacaine is about twice as toxic as lidocaine and a bit more than 4 times as toxic as chloroprocaine. Lidocaine, in turn, is twice as toxic as chloroprocaine. (Recall that toxicity is related inversely to $CD_{50}$ and $LD_{50}$: the lower the $CD_{50}$ or $LD_{50}$, the more toxic is the drug.)

## Discussion

We observed that a convulsant dose of local anesthetic is close to a lethal dose. This is most pronounced for bupivacaine and least pronounced for lidocaine. Thus a convulsion from bupivacaine is potentially 15 times more life-threatening than one from lidocaine under the conditions of this experiment. Although not studied here, these grim figures can be bettered considerably by vigorously treating convulsions. In one report, survival from a convulsant dose of local anesthetic was enhanced 2- to 4-fold by elementary cardiopulmonary resuscitation.[5] In another report, four of six dogs with procaine-induced convulsions died, while six ventilated littermates survived repeated procaine seizures.[6]

### Convulsions from Local Anesthetics

Confounding interpretation of older toxicity studies is that the incidence of lidocaine-induced convulsions in mice is nearly 6 times greater at 9 p.m. than at 3 p.m.[2] As a reasonably stable plateau is reached in the morning between 6 a.m. and 12 p.m., we did our experiments between 9 a.m. and 11 a.m. A time cycle of longer duration, the five-day estrus period of female mice, might also affect the convulsant threshold. Although there is no evidence to support that contention, we did house the mice five to a cage, and away from males, so as to induce anestrus.[1]

Our values for the $CD_{50}$ of lidocaine (111.0 mg/kg) given intraperitoneally were higher by about 50% than those observed by some others in mice: de Oliveira and Bretas,[7] for instance, reported a lidocaine $CD_{50}$ of 76.0 mg/kg in female mice. Still lower values have been reported for the lidocaine $CD_{50}$ in male mice, such as 70 mg/kg,[8] 65 mg/kg,[9] and 64 mg/kg.[10] Although variables such as sex, age, and time of day may have contributed, we attribute the difference between our results and those of others mainly to our sharper definition of "convulsions," as distinguished from running movements of the extremities. Running movements have only recently been recognized as a distinct phase in the spectrum of local anesthetic-induced central nervous system changes. Thus, Hofman and colleagues[11] found that running movements in dogs started after a mean intravenous lidocaine dose of 22.7 mg/kg, with tonic-clonic convulsions supervening only after half again that dose (total 33.3 mg/kg) had been given.

### Deaths from Local Anesthetics

Convulsions always precede death from local anesthetic overdosage, except when massive drug doses precipitate immediate circulatory collapse.[12] Although respiratory depression is thought to be the precipitating cause of death in rodents[2] (perhaps because cardiac function is difficult to evaluate in these small animals), we observed pallor more often than cyanosis, suggesting a direct myocardial effect of the local anesthetic as well.

Our value of 133.1 mg/kg for the lidocaine $LD_{50}$ in mice given intraperitoneal injections is quite close to the similarly obtained 142 mg/kg average (range 120 to 180 mg/kg) from six laboratories.[13] The intraperitoneal $LD_{50}$ for chloroprocaine (266.5 mg/kg) observed by us is likewise on the same order as that reported for procaine (200 mg/kg) in mice.[14] Comparable figures on the intraperitoneal $LD_{50}$ for bupivacaine in mice are not available (Dr. Ginette Jacob, Breon Laboratories, personal communication).

As was the case with local anesthetic-induced convulsions, age and sex also affect the lethality of local anesthetics. Young mice, for instance, tolerate more mepivacaine than middle-aged mice.[15] Whereas 75 mg/kg of cocaine given intraperitoneally was lethal in 53% of male mice, it was lethal in 74% of female mice.[16]

### Toxicity of Local Anesthetics

The intraperitoneal route of injection forces the anesthetic to enter the portal system, and thus pass through the liver, before reaching the systemic circulation. As chloroprocaine is hydrolyzed predominantly by plasma esterases, transhepatic passage probably does not substantially increase its biotransformation.[17] Biotransformation of the amide local anesthetics bupivacaine and lidocaine, conversely, is confined to hepatic enzyme systems. Since the (hepatic) metabolism of these drugs is quite slow, and since convulsions started within a minute or so of injection, we consider the toxic effects observed here to be attributable largely to unchanged lidocaine or bupivacaine. Extrapolation of our findings to man is enhanced by noting that the mouse is one of the few nonprimate species to hydrolyze procaine (and presumably also chloroprocaine) about as fast as does man.[18]

We can offer no ready explanation why bupivacaine-induced convulsions are potentially more lethal than convulsions induced by the other local anesthetics. Perhaps the high lipid solubility of bupivacaine causes it to bind firmly to the myocardium, thereby reducing cardiac efficiency.

Moore and colleagues,[19] in large clinical trials, found bupivacaine to be considerably less toxic in man than heretofore appreciated. Mainly based on work by Adams and associates[20] in female mice, bupivacaine is said to be about 4 times more toxic than lidocaine. Our results (also in female mice), however, show both the convulsant and the lethal doses of bupivacaine to be only about 2 times greater than those of lidocaine. Other than the fact that

Adams et al determined toxicity of the two drugs via the intravenous and subcutaneous routes, while we used the intraperitoneal route, we cannot explain the substantial discrepancy. In any case, our experimental observations support Moore's clinical observations that bupivacaine is less toxic than presently estimated. Perhaps upper dosage limits for bupivacaine based on presently available data have been set too low.

We conclude that convulsions from local anesthetic overdosage signal a potentially life-threatening complication because the margin between recovery and death from convulsions is slim. However, since support of respiration during the ictal and postictal periods reduces mortality severalfold, convulsions need not be a threat to life. We also conclude that bupivacaine is less toxic, relative to lidocaine, than heretofore recognized.

## ACKNOWLEDGMENTS

We thank Astra Pharmaceutical Products for supplying the lidocaine (Xylocaine), Breon Laboratories for the bupivacaine (Marcaine), and Pennwalt Corporation for the chloroprocaine (Nesacaine).

## REFERENCES

1. Whitten WK: Occurrence of anaestrus in mice caged in groups. J Endocrinol 18:102-107, 1959
2. Moore PA: Circadian variations in the convulsant response and pharmacokinetics of lidocaine. Thesis, University of Pittsburgh, 1977
3. Waud DR: On biological assays involving quantal responses. J Pharmacol Exp Ther 183:577-607, 1972
4. de Jong RH: Generalized analysis of quantal dose-response curves. Comput Biomed Res 6:588-595, 1973
5. Feinstein MB, Lenard W, Mathias J: The antagonism of local anesthetic induced convulsions by the benzodiazepine derivative diazepam. Arch Int Pharmacodyn 187:144-154, 1970
6. Mark LC, Brand L, Goldensohn ES: Recovery after procaine-induced seizures in dogs. EEG Clin Neurophysiol 16:280-284, 1964
7. de Oliveira LF, Bretas AD: Effects of 5-hydroxytryptophan, iproniazid, and p-chlorophenyl-alanine on lidocaine seizure threshold of mice. Eur J Pharmacol 29:5-9, 1974
8. Gangarosa LP, Hofman WF, Ross NM, et al: Local anesthetic drug reactions, in Third Symposium of Pharmacology, Therapeutic and Toxicology Group, International Association for Dental Research, Drug Interactions Vol 3. Edited by P Bourgault and N Ross. 1976, pp 18-35
9. Smudski JW, Sprecher RL, Elliott HW: Convulsive interactions of promethazine, meperidine and lidocaine. Arch Oral Biol 9: 595-600, 1964
10. Konthikamee W, Sprecher RL, Moore PA: Effects of acute and chronic administration of methylphenidate on lidocaine convulsions in mice. Arch Oral Biol 23:579-581, 1978
11. Hofman WF, Jerram DC, Gangarosa LP: Cardiorespiratory and behavioral reactions to the lidocaine-induced convulsion in the dog. Res Commun Chem Pathol Pharmacol 16:581-591, 1977
12. Covino BG: Pharmacology of newer local anesthetic agents, in Regional Anesthesia: Advances and Selected Topics. Edited by MDA Stanton-Hicks. Boston, Little, Brown & Co, 1978, pp 1-22
13. Wiedling S: Xylocaine: The Pharmacological Basis of Its Clinical Use. Second edition. Stockholm, Almqvist & Wiksell, 1964
14. Sanders HD: A comparison of the convulsant activity of procaine and pentylenetetrazol. Arch Int Pharmacodyn Ther 170: 165-177, 1967
15. Goldberg NB, Goldberg AF: Mepivacaine toxicity—the effect of ambient $P_{O_2}$ variation. Pharmacol Ther Dent 1:56-58, 1970
16. Evans MA, Harbison RD: Cocaine-induced hepatotoxicity in mice. Toxicol Appl Pharmacol 45:739-754, 1978
17. O'Brien JE, Abbey V, Hinsvark O, et al: Metabolism and measurement of chloroprocaine, an ester-type local anesthetic. J Pharm Sci 68:75-78, 1979
18. Reidenberg MM: Metabolism of procaine in serum of man and other species. Clin Res 19:354, 1971
19. Moore DC, Bridenbaugh LD, Thompson GE, et al.: Bupivacaine: A review of 11,080 cases. Anesth Analg 57:42-53, 1978
20. Adams HJ, Kronberg GH, Takman BH: Local anesthetic activity and acute toxicity of (±)-2-(N-ethylpropylamino)-2′,6′-butyroxylidide, a new long-acting agent. J Pharm Sci 61:1829-1831, 1972

ANESTH ANALG
59:406–409, 1980

# Ketamine Suppression of Chemically Induced Convulsions in the Two-Day-Old White Leghorn Cockerel

**Barry S. Reder, DDS,* Larry D. Trapp, DDS, MS,† and Kenneth C. Troutman, DDS, MPH‡**

REDER, B. S., TRAPP, L. D., AND TROUTMAN, K. C.: Ketamine suppression of chemically induced convulsions in the two-day-old white leghorn cockerel. Anesth Analg 59:406–409, 1980.

Ketamine has been evaluated for convulsant properties in animals and humans with contradictory results. The present investigation evaluated the convulsant properties of ketamine in a previously unreported animal model. Two-day-old chicks were selected as test animals because they have incomplete blood-brain barriers and thus greater penetrance of xenobiotics affecting the central nervous system. Control and experimental animals were given a central nervous system stimulant, pentylenetetrazol (Metrazol) at a dosage level (100 mg/kg) causing convulsions in 90% of animals. The effect of ketamine pretreatment was then observed for the: (1) number of animals convulsing; (2) time of onset of convulsions; and (3) mortality. Ketamine (100 mg/kg) significantly decreased the number of animals that convulsed and decreased mortality; 10 mg/kg of ketamine significantly prolonged the time of onset of convulsions. This study does not support the conclusion that ketamine is a convulsant. Ketamine has significant anticonvulsant properties in the young chick model.

**Key Words:** ANESTHETICS, Intravenous: ketamine; ANTICONVULSANTS: ketamine; BRAIN: convulsions.

THE ROLE of ketamine in anesthesia is gradually being defined,[1-6] and a complete review of the drug is available.[7] One pharmacologic property of ketamine that remains controversial, however, is the central nervous system (CNS) effect of the drug in individuals with convulsive disorders. Specifically, does ketamine induce clinical seizures in individuals with preexisting seizure disorders?

The intrinsic convulsant properties of ketamine in normal animals as well as in animals with induced seizures and seizure foci have been investigated in several studies.[8-11] Ketamine has, for example, been reported as not producing observable convulsions in normal animals, although increases in motor activity have been reported.[8-10] Electroencephalographic (EEG) data, although not in total agreement, generally demonstrate selective stimulation of the CNS in normal cats.[9,11] Studies of the effect of ketamine on responses to epileptogenic stimuli, including electricity, cobalt-gelatin implantation in the CNS, pentylenetetrazol (Metrazol) by systemic injection, penicillin implanted in the CNS, and strychnine by systemic injection have, however, given conflicting results in experimental animals.[8,10,12] Both protection against such stimuli and a lowering of seizure threshold have been reported.

---

* Resident in Pediatric Dentistry, Division of Pediatric Dentistry, Department of Dentistry, Harbor-UCLA Medical Center.

† Assistant Professor of Anesthesiology, Schools of Dentistry and Medicine, University of California at Los Angeles, Harbor-UCLA Medical Center.

‡ Associate Professor of Pediatric Dentistry, University of California at Los Angeles, Harbor-UCLA Medical Center.

Received from the Departments of Anesthesiology and Dentistry, Harbor-UCLA Medical Center, 1000 W Carson St, Torrance, California 90509. Accepted for publication February 12, 1980.

Reprint requests to Dr. Trapp, Department of Anesthesiology.

Studies of the convulsant properties of ketamine in humans have also been contradictory.[11, 13-23] A recent review[24] states unequivocally that ketamine is a convulsant agent, whereas a contradictory study[23] found natural sleep to be a more potent stimulator of convulsions than ketamine in the epileptic patient.

The purpose of the present study is to provide further information on which to base the neuropharmacologic characterization of ketamine using an animal model in which the blood-brain barrier is poorly developed,[25] thereby allowing dissociation of the effects of changes in penetrance of drugs into the CNS from intrinsic direct effects of drugs on central neuronal tissues.

## Methods

All experiments were performed using white leghorn cockerels, 2 to 3 days old, weighing between 30 and 45 g each. The animals were fed and given water ad libitum until the first injection was administered. The chicks were then fasted for the observations which usually lasted less than 3 hours. All experiments were performed at the same time of the day at the same ambient room temperature of 21-22 C.[26] Each chick was weighed before administering the injection and all drug doses were based on body weight.

All drugs were administered by intraperitoneal injection using injection volumes of 0.5 ml or less. Animals were eliminated if blood or gastrointestinal contents were aspirated before injection. A convulsion was defined as clonic motor activity immediately followed by tonic extension of the body.

With the exception of the phenobarbital dose-response data, each experiment was performed in a group of 10 chicks, with another group of 10 chicks acting as controls. The following studies were made: (1) dose-response curves for ketamine were constructed using 1, 10, 100, and 1000 mg/kg, with control chicks receiving an equal volume of saline; (2) pentylenetetrazol (PTZ) dose-response curves were determined using 50, 100, and 200 mg/kg with control animals receiving saline; (3) the effect of ketamine pretreatment on PTZ-induced seizures was evaluated by injecting ketamine (1, 10, and 100 mg/kg) followed 2 minutes later by PTZ (100 mg/kg); controls received saline pretreatment; and (4) the effect of phenobarbital pretreatment on PTZ-induced seizures was evaluated by injecting phenobarbital (20 mg/kg) followed 5 minutes later by PTZ (100 mg/kg); controls received pretreatment with saline.

Evaluation of the dose-response to ketamine was performed primarily by observation of the loss of righting reflex. Other behavioral variables observed were postinjection defecation, overall changes in motor activity, and an intermittent sleep-like state.

The dose-response to PTZ was evaluated by observation of convulsions. The dose of PTZ that caused 90% of the animals to convulse ($CD_{90}$) was then used in the study.

The effect of pretreatment on PTZ-induced convulsions was evaluated by observation of: (1) incidence of convulsions, (2) time of onset of convulsions, and (3) mortality rates of chicks 3 hours after injection of PTZ. Since not all chicks receiving PTZ convulsed, the experimental groups for the second category contained fewer than ten animals. Means and standard deviations of the data were computed.

Statistical significance of the differences was analyzed using a two-sample independent *t*-test for the time delay to convulsions and Fisher's exact test, two-tailed probability, for the frequency of convulsions and death. All animals were treated in a humane manner at least equal to the standards described by the American Physiological Society.

## Results

### Dose-Response Curves for Ketamine

Chicks given 1 mg/kg of ketamine showed no behavioral differences when compared with control chicks. After 10 mg/kg of ketamine, five of ten chicks showed transient loss of righting reflex commencing within about 90 seconds. Two minutes later all ten chicks were behaviorally indistinguishable from control animals given saline. All chicks given 100 mg/kg of ketamine lost their righting reflexes approximately 60 seconds after injection of ketamine. This last group of chicks exhibited a continuous "bike pedaling" activity with occasional tonic extension of the wings. Loss of righting reflex was noted at 35 seconds in all chicks receiving 1000 mg/kg of ketamine. This was also followed by hypermotor activity, as above. Although mortality was zero for 1, 10, and 100 mg/kg of ketamine, all of the chicks receiving 1000 mg/kg of ketamine were dead within 1 hour. Clonic-tonic seizures were not observed at any dosage level.

### Dose-Response Data for Pentylenetetrazol

Pentylenetetrazol (100 mg/kg) caused clonic-tonic convulsions in nine (90%) of the 10 chicks in the test group ($CD_{90}$) and was selected as the drug dosage to be used in the remaining tests. Mortality was 80% in this group of chicks.

### Phenobarbital Pretreatment and Pentylenetetrazol-Induced Convulsions

None of 10 chicks given phenobarbital (20 mg/kg) convulsed following pentylenetetrazol (100 mg/kg) while nine of 10 control animals given saline convulsed. Mortality rates were not recorded for this portion of the investigation.

### Ketamine Pretreatment and Pentylenetetrazol-Induced Convulsions

With pretreatment of 1 mg/kg of ketamine, nine of 10 chicks convulsed after 100 mg/kg of pentylenetetrazol (Figure). Eight of 10 control chicks with saline pretreatment convulsed. With 10 mg/kg of ketamine, six of 10 chicks convulsed, and eight of 10 control chicks convulsed. At 100 mg/kg of ketamine, no convulsions were observed in 10 chicks, and nine of 10 saline pretreatment control chicks convulsed. At 100 mg/kg of ketamine the difference between treatment and control groups was statistically significant ($p < 0.001$). The remaining treatments did not have statistically significant effects.

### Time Delay to Convulsion (TDC)

Chicks receiving 1 mg/kg of ketamine pretreatment had a mean TDC of 2.8 ± 1.4 minutes (Table 1). Saline pretreatment controls had a mean TDC of 3.1 ± 2.5 minutes. The difference was not statistically significant. After 10 mg/kg of ketamine, chicks had a mean TDC of 54.7 ± 23.1 minutes, and the TDC of saline control animals was 6.6 ± 6.0 minutes. The difference was statistically significant ($p < 0.001$). Since no chicks receiving 100 mg/kg of ketamine convulsed, no comparison can be made with the saline control TDC value of 4.3 ± 2.5 minutes.

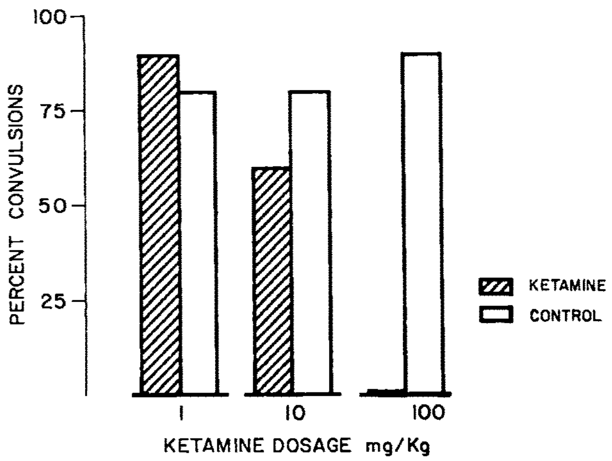


FIGURE. Dose-response of ketamine in the suppression of pentylenetetrazol-induced convulsions in the 2-day-old chick.

**TABLE 1**

**Dose-Response of Ketamine Pretreatment on Elapsed Time to Convulsions Induced with Intraperitoneal Pentylenetetrazol in Two-Day-Old Chicks**

| Ketamine dose | Elapsed time to convulsion* | p value |
|---|---|---|
| | min | |
| 1.0 mg/kg (N = 9) | 2.8 ± 1.4 | NS† |
| Control (N = 8) | 3.1 ± 2.5 | |
| 10.0 mg/kg (N = 6) | 54.7 ± 23.1 | 0.001 |
| Control (N = 8) | 6.6 ± 6.0 | |
| 100.0 mg/kg (N = 0) | No convulsions | —‡ |
| Control (N = 9) | 4.33 ± 2.5 | |

* Values are means ± SD.
† Not statistically significant.
‡ —Tests for significance not applicable.

**TABLE 2**

**Protection by Ketamine from Death after intraperitoneal Pentylenetetrazol (100 mg/kg) in Two-Day-Old Chicks**

| Ketamine dose | Mortality | p value |
|---|---|---|
| | % | |
| 10.0 mg/kg (N = 10) | 0 | 0.09 |
| Control (N = 10) | 40 | |
| 100.0 mg/kg (N = 10) | 0 | 0.001 |
| Control (N = 10) | 80 | |

### Protection from Death

None of the chicks that received pretreatment with 10 mg/kg of ketamine died; four of the saline pretreatment controls died. The difference was not statistically significant ($p = 0.09$( (Table 2). At 100 mg/kg of ketamine, none of the chicks receiving ketamine died; eight control animals given saline were dead by 3 hours after receiving the injection. The difference was statistically significant ($p < 0.001$).

## Discussion

Ketamine has been studied in mice, rats, cats, monkeys, and humans to elucidate the drug's effect in patients with seizure disorders.[10,12,23] This study was undertaken to evaluate the effect of ketamine on induced seizures in yet another species and thereby provide new information to an otherwise contradictory pharmacologic characterization. Earlier investigations which stressed the subject's EEG response to ketamine have been criticized due to the lack of clinical seizure correlation.[23] The present study relies only on behavioral observations with relatively clear end points.

The 2-day-old chick model was selected for its incomplete blood-brain barrier and the resultant greater permeability and response to many xenobiotics.[26] The existence of brain damage and possible associated blood-brain barrier permeability changes may be uncontrolled variables in human subjects causing disparate results reported in the literature. The 2-day-old chick model can be conceptually viewed as a test animal with a pharmacologic "window" incorporated in the CNS blood-brain barrier. CNS penetrance is thereby reduced in significance as a varible in drug studies analyzing CNS response. We believe this model may provide more consistent pharmacologic responses within the CNS, and thereby reduce the contradictory characterizations referred to above.

Our results indicate that ketamine does not induce seizures in subanesthetic or anesthetic doses in the chick model, although increased motor activity was observed with 100 mg/kg of ketamine. Furthermore, ketamine afforded protection from pentylenetetrazol-induced convulsions. We recognize that the dose of ketamine providing significant protection from seizures (100 mg/kg) is substantially larger than those doses utilized in clinical medicine. Differences in doses can be attributed to species variability and routes of administration.[10, 12] The demonstration of phenobarbital protection against convulsions in the chick model illustrates the analogy between the chick model and the clinical situation.[27]

Consideration of the clinical applicability of these data leads to the hypothesis that any convulsant properties of ketamine may be related to the area(s) within the CNS stimulated by the drug (e.g., those areas related to wing extension in the chick). Thus, if a lesion, diagnosed or undiagnosed, coincides with the area stimulated by ketamine, clinical convulsions may ensue. If a lesion and the area stimulated by ketamine do not coincide, ketamine may protect against clinical seizure activity by a mechanism not yet elucidated.

## ACKNOWLEDGMENT

The pentylenetetrazol was provided by Mr. H. Graham of Knoll Pharmaceutical Company.

## REFERENCES

1. Page, P, Morgan M, Loh L: Ketamine anesthesia in pediatric procedures. Acta Anaesthesiol Scand 16:155-160, 1972
2. Cohenour K, Gamble JW, Metzger MT, et al: A composite general anesthesia technique using ketamine for pediatric outpatients J Oral Surg 36:594-598, 1978
3. Weis FF, Cho CH: Ketamine for induction of anesthesia in the severely retarded. Anesthesiol Rev 2:35-36, 1975
4. O'Brien DN, Kim KC: An evaluation of ketamine, droperidol and nitrous oxide in pedodontic outpatients. J Dent Child 42: 31-36, 1975
5. Kaplan B, Hirschowitz AS: The dental treatment of problem children under ketamine anaesthesia. S Afr Med J 49:313-314, 1975
6. Sussman DR: A comprehensive evaluation of ketamine anesthesia in children and adults. Anesthesiology 40:459-464, 1974
7. Dundee JW, Wyant GM: Intravenous Anaesthesia: Edinburgh, Churchill Livingstone Co, 1974, pp 219-247
8. Chen G, Ensor CR, Bohner B: The neuropharmacology of 2-(O-chlorophenyl)-2-methylaminocyclohexanone hydrochloride. J Pharmacol Exp Ther 152:332-229, 1966
9. Kayama Y, Iwama K: The EEG, evoked potentials, and single unit activity during ketamine anesthesia in cats. Anesthesiology 36:316-328, 1972
10. Celesia GG, Chen RC: Effects of ketamine on EEG activity in cats and monkeys. Electroencephalogr Clin Neurophysiol 37: 345-35[illegible], 1974
11. Corssen G, Miyosaka M, Domino EF: Changing concepts in pain control during surgery: dissociative anesthesia with CI-581, a progress report. Anesth Analg 47:746-757, 1968
12. DeVore GR, McQueen JR, Woodbury DM: Ketamine hydrochloride and its effect on a chronic epileptic cortical focus. Epilepsia 17:111-117, 1976
13. Corssen G, Little SC, Tavakoli M: Ketamine and epilepsy. Anesth Analg 53:319-335, 1974
14. Young RA, Epker BN: Ketamine hydrochloride in out-patient oral surgery in children. J Oral Surg 29:703-705, 1971
15. Sobczak OM: Use of ketamine in pediatric dentistry. Anesth Analg 54:248-249, 1975
16. Winters WD: Epilepsy or anesthesia with ketamine. Anesthesiology 36:309-311, 1972
17. Radnay PA, Badola RP: Generalized extensor spasm in infants following ketamine anesthesia. Anesthesiology 39:459-460, 1973
18. Elliott E, Hanid TK, Arthur LJ, et al: Ketamine anaesthesia for medical procedures in children. Arch Dis Child 51:56-59, 1976
19. Thompson GE: Ketamine induced convulsions. Anesthesiology 37:662-663, 1972
20. Bennet DR, Madsen JA, Jordan WS, et al: Ketamine anesthesia in brain damaged epileptics. Neurology 23:449-460, 1973
21. Ferrer-Allado T, Brechner VL, Dymond A, et al: Ketamine induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333-334, 1973
22. Madsen JA, Bennett DR, Jordan WS, et al: A comparative study of ketamine hydrochloride and thiopental in brain damaged persons with epilepsy. Neurology 24:386, 1974
23. Celsia GG, Chen RC, Bamforth BJ: Effects of ketamine in epilepsy. Neurology 25:169-172, 1975
24. Steen PA, Michenfelder JD: Neurotoxicity of anesthetics. Anesthesiology 50:437-453, 1979
25. Spooner CE, Winters WD: Neuropharmacological profile of the young chick. Int J Neuropharmacol 5:217-236, 1966
26. Giedt WR, Lakin ML, Winters WD: Diurnal response to ketamine and gamma-hydroxybutyrate and its possible relationship to pineal indoleamines. Neuropharmacology 17:221-228, 1978
27. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fourth edition. New York, MacMillan Co, 1971, p 353

ANESTH ANALG
59:410-416, 1980

# Arrhythmogenic Effects of Aminophylline during Halothane Anesthesia in Experimental Animals

**Joseph A. Stirt, MD,* Jack M. Berger, MD, PhD,† Sandra M. Ricker, BS,‡ and Stuart F. Sullivan, MD§**

---

STIRT, J. A., BERGER, J. M., RICKER, S. M., AND SULLIVAN, S. F.: Arrhythmogenic effects of aminophylline during halothane anesthesia in experimental animals. Anesth Analg 59:410–416, 1980.

Arrhythmogenic effects of aminophylline (theophylline ethylenediamine) during halothane anesthesia have been reported but have not been related to serum theophylline levels. This study was designed to determine the arrhythmogenicity of therapeutic and toxic serum theophylline levels during halothane anesthesia. The study consisted of three parts. In part 1 (induction) six dogs were anesthetized for 15 minutes with 1% halothane in air and then given intravenous aminophylline, 50 mg/kg. In part 2 (maintenance) eight dogs were anesthetized for 2 hours with 1% halothane and then given intravenous aminophylline, 10 mg/kg. In part 3, after four additional hours of steady-state 1% halothane anesthesia, additional intravenous aminophylline, 25 mg/kg, was given to these eight animals. Three of six dogs in part 1 had arrhythmias following aminophylline, with serum theophylline levels ranging from 48 to 66 mg/L. No dog in part 2 had arrhythmias following the 10 mg/kg dose of aminophylline, with serum theophylline levels of 14 to 23 mg/L. Six of eight dogs in part 3 had arrhythmias shortly after aminophylline, 25 mg/kg, with serum theophylline levels of 36 to 72 mg/L. Aminophylline administration after prolonged 1% halothane anesthesia appears free from arrhythmogenic effects if serum theophylline levels remain near the therapeutic range (10 to 20 mg/L). Aminophylline administration resulting in high serum theophylline levels (above 36 mg/L) causes ventricular arrhythmias when aminophylline is given during induction or maintenance of 1% halothane anesthesia. Arrhythmias usually (89%) begin within 5 minutes of aminophylline administration, and these arrhythmias always resolve spontaneously within 2 minutes of onset.

**Key Words:** PHARMACOLOGY: Aminophylline; ANESTHETICS, Volatile: halothane; HEART: arrhythmias.

---

AMINOPHYLLINE (theophylline ethylenediamine) has been used for treating asthma since 1937.[1] Halothane is considered to be an anesthetic agent of choice for the asthmatic patient.[2-4] The concurrent use of these two drugs has been shown to produce severe ventricular arrhythmias in experimental animals.[5-7] More recently, cardiac arrhythmias have been observed in patients receiving aminophylline and subsequently anesthetized with halothane,[8, 9] raising doubts about the safety of using aminophylline and halothane together. On the other hand, an anecdotal report[10] noted no problems associated with their use in combination.

Therapeutic and toxic serum theophylline levels have been well defined in conscious humans, [11, 12] but no correlation between drug levels and arrhythmogenic effects during anesthesia has been made. We

---

* Resident and Research Fellow.

† Research Associate.

‡ Technical Services Supervisor.

§ Professor.

Supported by a grant from the UCLA Department of Anesthesiology.

Received from the Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California 90024. Accepted for publication February 20, 1980.

Reprint requests to Dr. Stirt.

previously reported[13] that therapeutic aminophylline doses caused a small increase in heart rate but had no other adverse effects on cardiorespiratory function during prolonged halothane anesthesia in dogs. In this three-part study we report on the arrhythmogenic effects of aminophylline at measured serum theophylline concentrations in the therapeutic and toxic range during the induction and maintenance of halothane anesthesia in dogs.

## Methods and Materials

Studies were conducted in six dogs weighing between 14.5 and 23 kg (average weight 18.2 kg) in part 1. Eight other dogs weighing between 18.5 and 23.5 kg (average weight 21.5 kg) were used in parts 2 and 3.

### Part 1

In this series all dogs were initially anesthetized with intravenous sodium thiopental, 20 mg/kg. The animals were then intubated with cuffed orotracheal tubes and air-tight fits secured. Using a non-rebreathing valve and Harvard animal respirator, controlled ventilation was begun with 1% halothane in air at 12 breaths per minute. End-tidal carbon dioxide concentration was adjusted to approximately 4.5% by appropriate modification of the tidal volume, and no further adjustments in ventilation were made. A continuous lead II electrocardiogram was recorded.

Systolic, diastolic, and mean arterial blood pressures were measured from a femoral artery catheter connected to a pressure transducer (Bentley Trantec, Irvine, CA). Heart rate was calculated from the arterial pressure trace recording. Arterial blood samples were obtained from the femoral artery catheter using heparinized glass syringes, and iced immediately. Oxygen tension ($P_{O_2}$), carbon dioxide tension ($P_{CO_2}$), and pH were measured in duplicate in all samples (model 313 blood gas analyzer, Instrumentation Laboratories, Inc, Boston, MA). Using an open-circuit technique, exhaled gas was directed into a modified electronic volume displacement spirometer (model 220 spirometer, Cardiopulmonary Instruments, Inc, Houston, TX) and analyzed for halothane concentration by a gas mass spectrometer (MGA-1100, Perkin-Elmer Corp, Pomona, CA). Body temperature was measured by a thermistor placed in the lower third of the esophagus, and was maintained between 37–38 C throughout the study with a heating lamp and blanket. An intravenous infusion of 0.9% NaCl at 100 ml/hr was maintained for the duration of the study (30 minutes following completion of aminophylline administration).

After 15 minutes of 1% halothane anesthesia, aminophylline (Invenex, Chagrin Falls, Ohio), 50 mg/kg, was administered via intravenous infusion over 5 minutes. Theophylline levels were determined in duplicate in all arterial blood samples by homogenous enzyme immunoassay (EMIT, Syva, Palo Alto, CA), in which competitive protein binding was determined spectrophotometrically using a labeled enzyme and specific binding antibody.[14] Serum theophylline and arterial blood gases were determined 2 minutes following aminophylline in all animals, and at the time arrhythmias occurred. Potassium and ionized calcium values were determined 5 minutes before (control) and 30 minutes after aminophylline administration in all animals, and at the time arrhythmias occurred.

### Part 2

All eight dogs were initially anesthetized with intravenous sodium pentobarbital, 30 mg/kg. All subsequent monitoring and anesthesia maintenance was performed exactly as in part 1. Two hours were allowed to elapse before administration of aminophylline, 10 mg/kg, as a 5-minute intravenous infusion. Arterial blood samples were obtained 5 minutes before and 2 minutes following aminophylline infusion, and analyzed for $P_{O_2}$, $P_{CO_2}$, pH, and theophylline levels. The lead II electrocardiogram was continuously monitored and recorded for the next 4 hours.

### Part 3

Beginning 4 hours after the initial 10-mg/kg aminophylline infusion, each of the eight animals studied in part 2 received a 30-second intravenous infusion of aminophylline, 25 mg/kg. Arterial blood samples for $P_{O_2}$, $P_{CO_2}$, pH, and serum theophylline levels were obtained 5 minutes prior to the 25-mg/kg dose, and samples for determination of serum theophylline levels were obtained 5 minutes following completion of the infusion. This portion of the study lasted 30 minutes following completion of the 25 mg/kg aminophylline infusion.

## Results

### Part 1: Halothane Induction

Mixed-expired halothane concentration just prior to aminophylline administration (50 mg/kg) averaged 0.72 ± 0.04% (mean ± SE) in animals that subsequently developed arrhythmias, and 0.76 ± 0.02% in animals that did not develop arrhythmias. Heart rate increased from 141 ± 12 to 194 ± 11 beats per minute and mean arterial pressure decreased from 77 ± 17 to 61 ± 12 torr 2 minutes following aminophylline administration (Table 1). Three of six dogs given aminophylline, 50 mg/kg, over 5 minutes after 15 minutes of 1% halothane developed arrhythmias (Table 1). Serum theophylline levels at the time arrhythmias occurred ranged from 48 to 66 ml/L, while peak levels in animals that did not develop arrhythmias ranged from 57 to 81 mg/L. Arterial $P_{O_2}$, $P_{CO_2}$, and pH at the time arrhythmias occurred are listed in Table 2, along with serum theophylline concentrations. Ionized calcium values before, during, and after arrhythmias are also listed in Table 2, along with serum potassium.

Of the three dogs with arrhythmias, in two the arrhythmias developed during infusion of aminophylline. The arrhythmias consisted of junctional rhythm in one and bigeminy in the other; both resolved spontaneously in 60 seconds and 10 seconds, respectively, before completion of aminophylline administration (Table 1). No arrhythmias recurred in either animal. In the third dog the arrhythmia had a delayed onset (16 minutes after beginning aminophylline) and consisted of multifocal premature ventricular contractions (PVCs) at a rate of 30 per minute. PVCs continued for 3 minutes, followed by bigeminal rhythm which failed to resolve.

## Part 2: Halothane Maintenance (2 Hours)

Mixed-expired halothane concentration averaged 0.81 ± 0.01% just before the 10 mg/kg aminophylline infusion. Of eight dogs given aminophylline, 10 mg/kg, over 5 minutes after 2 hours of 1% halothane, none developed arrhythmias at any time in the 4 hours following aminophylline administration. Peak serum theophylline levels ranged from 14 to 23 mg/L. Values for blood pressure, heart rate, $P_{O_2}$, $P_{CO_2}$, and pH 5 minutes before and 2 minutes after aminophylline administration are shown in Table 3, as well as serum theophylline levels 2 minutes following aminophylline.

**TABLE 1**

**Arrhythmias following Aminophylline (50 mg/kg IV) Administered 15 Minutes after Induction of Halothane Anesthesia: Time and Duration***

| Dog | Arrhythmia | Time until onset | Duration | HR | | BP | | MAP | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Before | After | Before | After | Before | After |
| | | *min* | *min* | *beats/min* | | *torr* | | *torr* | |
| 1 | — | — | — | 102 | 156 | 100/55 | 70/40 | 60 | 45 |
| 2 | Junctional | 3.5 | 1 | 126 | 222 | 95/55 | 70/60 | 65 | 65 |
| 3 | — | — | — | 174 | 216 | 100/50 | 55/30 | 65 | 40 |
| 4 | — | — | — | 174 | 186 | 80/40 | 60/30 | 50 | 40 |
| 5 | Bigeminy | 4.5 | 0.2 | 132 | 210 | 200/140 | 145/115 | 160 | 120 |
| 6 | PVCs, bigeminy | 16.0 | 19+ | 138 | 174 | 80/55 | 75/50 | 60 | 55 |

* Heart rate (HR), arterial blood pressure (BP), and mean arterial blood pressure (MAP) 5 minutes before and 2 minutes after administration of aminophylline.

**TABLE 2**

**Arrhythmias following Aminophylline (50 mg/kg IV) Administered 15 Minutes after Induction of Halothane Anesthesia: Serum Theophylline and Arterial Blood Gases***

| Dog | Arrhythmia | Theophylline | $P_{O_2}$ | $P_{CO_2}$ | pH | $Ca^{2+}$ | | | $K^+$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Before | During | After | Before | During | After |
| | | *mg/L* | *torr* | *torr* | | | *meq/L* | | | *meq/L* | |
| 1 | — | 57 | 102 | 28 | 7.40 | 2.45 | — | 2.33 | 4.7 | — | 4.2 |
| 2 | Junctional | 51 | 96 | 28 | 7.45 | 2.27 | 2.32 | 2.21 | 3.5 | 3.3 | 2.6 |
| 3 | — | 75 | 83 | 26 | 7.43 | 2.25 | — | 2.32 | 3.5 | — | 3.4 |
| 4 | — | 81 | 98 | 27 | 7.43 | 2.38 | — | 2.36 | 3.6 | — | 2.6 |
| 5 | Bigeminy | 66 | 77 | 23 | 7.48 | 2.11 | 2.15 | 2.21 | 3.4 | 3.6 | 3.5 |
| 6 | PVCs, bigeminy | 48 | 92 | 27 | 7.44 | 2.14 | 2.16 | 2.25 | 3.2 | 3.2 | 3.3 |

* Values are those at the time arrhythmias occurred. When no arrhythmia occurred, values listed are those 2 minutes following aminophylline administration. Control ionized calcium and potassium values are recorded (Before), at the time arrhythmias occurred (During), and 30 minutes following aminophylline (After).

**TABLE 3**

**Mean Arterial Blood Pressure (MAP), Heart Rate (HR), and Arterial Blood Gas Values 5 Minutes before and 2 Minutes after Aminophylline (10 mg/kg IV) Given 2 Hours after Induction of Halothane Anesthesia***

| Dog | Theophylline | MAP | | HR | | $P_{O_2}$ | | $P_{CO_2}$ | | pH | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before | After | Before | After | Before | After | Before | After | Before | After |
| | *mg/L* | *torr* | | *beats/min* | | *torr* | | *torr* | | | |
| 1 | 20.0 | 130 | 110 | 180 | 180 | 90 | 91 | 34 | 32 | 7.42 | 7.43 |
| 2 | 22.5 | 85 | 70 | 120 | 144 | 73 | 73 | 36 | 35 | 7.32 | 7.32 |
| 3 | 23.0 | 85 | 80 | 132 | 144 | 86 | 88 | 34 | 31 | 7.31 | 7.32 |
| 4 | 15.0 | 95 | 70 | 108 | 120 | 87 | 89 | 31 | 34 | 7.35 | 7.35 |
| 5 | 18.0 | 95 | 105 | 126 | 144 | 78 | 80 | 34 | 35 | 7.39 | 7.39 |
| 6 | 22.0 | 80 | 75 | 120 | 132 | 76 | 74 | 33 | 34 | 7.38 | 7.37 |
| 7 | 14.0 | 65 | 65 | 120 | 144 | 81 | 80 | 32 | 31 | 7.35 | 7.35 |
| 8 | 20.0 | 70 | 55 | 126 | 132 | 85 | 88 | 39 | 39 | 7.28 | 7.27 |

* Theophylline levels 2 minutes after aminophylline are also shown. No arrhythmias occurred.

## Part 3: Halothane Maintenance (6 Hours)

The same eight dogs used in part 2 were given aminophylline, 25 mg/kg, beginning 240 minutes after their initial 10 mg/kg dose. At the time of the 25 mg/kg dose, mixed-expired halothane concentration averaged 0.88 ± 0.02% in animals that subsequently developed arrhythmias and 0.87 ± 0.08% in animals that did not develop arrhythmias. Arterial $P_{O_2}$ just before aminophylline administration ranged from 73.0 to 90.3 torr; arterial $P_{CO_2}$ ranged from 26.6 to 41.1 torr, and arterial ph from 7.21 to 7.38 (Table 4). Six of eight dogs developed arrhythmias during the 30 minutes immediately following aminophylline. Theophylline values at the time arrhythmias first occurred ranged from 36 to 72 mg/L (Table 4). In the two animals that showed no arrhythmic activity peak theophylline levels were 48 and 54 mg/L.

Heart rate increased from 130 ± 10 to 173 ± 18 beats per minute and mean arterial pressure decreased from 89 ± 9 to 58 ± 9 torr 5 minutes following aminophylline administration (Table 5). Of the six animals with arrhythmias, four had unifocal PVCs ranging in frequency from 2 to 4 per minute and two had junctional rhythm. In all six animals arrhythmias first developed within 4.5 minutes of aminophylline; all arrhythmias spontaneously resolved within 2 minutes of their appearance (Table 5).

**TABLE 4**

**Arrhythmias following Aminophylline (25 mg/kg IV) 4 Hours after Initial Dose (10 mg/kg IV): Serum Theophylline Concentrations***

| Dog | Arrhythmia | Theophylline | | $P_{O_2}$ | $P_{CO_2}$ | pH |
|---|---|---|---|---|---|---|
| | | Before | After | | | |
| | | *mg/L* | | *torr* | *torr* | |
| 1 | PVCs | 9.3 | 72 | 90 | 27 | 7.38 |
| 2 | PVCs | 6.0 | 60 | 65 | 41 | 7.21 |
| 3 | — | 10.0 | 54 | 73 | 32 | 7.35 |
| 4 | — | 5.0 | 48 | 82 | 33 | 7.34 |
| 5 | Junctional | 8.5 | 60 | 90 | 32 | 7.41 |
| 6 | Junctional | 9.0 | 60 | 84 | 36 | 7.31 |
| 7 | PVCs | 6.5 | 42 | 73 | 29 | 7.34 |
| 8 | PVCs | 7.0 | 36 | 79 | 39 | 7.21 |

* Values are for concentrations 5 minutes before and 5 minutes after aminophylline (25 mg/kg) and arterial blood gas values 5 minutes before aminophylline (25 mg/kg).

## Discussion

Cardiac arrhythmias result from a disturbance of the normal repetitive sequence of electromechanical events involved in myocardial contraction. Nonuniformity of recovery following excitation favors the fractionation of impulses arising during the relative refractory period, and increases the chance of reentry; any drug that increases the temporal dispersion or asynchrony of excitability recovery increases the likelihood of arrhythmia.[15] Catecholamines administered intravenously have been shown to increase dispersion of the ventricular refractory period.[16]

Catecholamines have long been known to predispose to arrhythmias in unanesthetized patients.[17] In the presence of halothane, the dose of catecholamine required to produce an arrhythmia is markedly decreased.[18] Aminophylline has been found to increase urinary excretion of epinephrine and norepinephrine in man.[19] Further studies have shown that it directly stimulates synthesis and release of catecholamines from the adrenal medulla.[20–22] Aminophylline may also cause release of endogenous myocardial catecholamine stores.[23]

Studies of aminophylline and ventricular fibrillation threshold have revealed that epinephrine and

**TABLE 5**

**Arrhythmias following Aminophylline (25 mg/kg IV) Given 4 Hours after Initial Dose (10 mg/kg IV): Time and Duration***

| Dog | Arrhythmia | Time until onset | Duration | HR | | MAP | |
|---|---|---|---|---|---|---|---|
| | | | | Before | After | Before | After |
| | | *min* | *min* | *beats/min* | | *torr* | |
| 1 | PVCs | <0.1 | 0.5 | 162 | 180 | 105 | 65 |
| 2 | PVCs | <0.1 | 0.5 | 144 | 186 | 95 | 50 |
| 3 | — | — | — | 162 | 186 | 115 | 90 |
| 4 | — | — | — | 150 | 156 | 95 | 60 |
| 5 | Junctional | 4.5 | 0.5 | 138 | 162 | 100 | 85 |
| 6 | Junctional | 1.0 | 0.5 | 108 | 144 | 95 | 55 |
| 7 | PVCs | 1.0 | 1.5 | 162 | 174 | 45 | 20 |
| 8 | PVCs | 1.5 | 2.0 | 156 | 198 | 65 | 40 |

* Heart rate (HR) and mean arterial blood pressure (MAP) 5 minutes before and 5 minutes following aminophylline administration.

aminophylline have similar effects on induction of severe ventricular arrhythmias, with both epinephrine and aminophylline causing an approximate 30% to 40% decrease in ventricular fibrillation threshold during adequate oxygenation and ventilation.[16, 24] In these studies aminophylline was administered over a 20- to 30-minute period, and the decrease in fibrillation threshold occurred only during the infusion, lasting for 20 to 30 minutes.[24] The authors attributed this to nonuniform myocardial distribution of aminophylline which resolved following drug administration, the subsequent stable blood and myocardial cell theophylline level making induction of arrhythmias more difficult.[24]

Several views currently exist regarding the mechanism of arrhythmogenesis by aminophylline. Many believe the primary action of aminophylline is the intracellular inhibition of phosphodiesterase, an enzyme which causes the breakdown of cyclic adenosine monophosphate (AMP) to 5′-AMP.[25] The decrease in phosphodiesterase results in elevation of intracellular cyclic AMP. Subsequently cyclic AMP may activate cardiac phosphorylase from its inactive form, stimulating glycogenolysis in the conducting system.[26] This would result in myocardial intracellular voltage shifts, causing susceptibility to arrhythmias.[27] The similarity of the effects of aminophylline and catecholamines on arrhythmias may stem from the fact that catecholamines, by activating adenyl cyclase, also stimulate the production of cyclic AMP with the same resulting effects on the conducting system.[26]

A second school of thought proposes that aminophylline acts on myocardial contractility by altering calcium kinetics.[28] Theophylline has been found to enter myocardial tissue very rapidly.[29] It has been suggested that aminophylline has two effects on excitation-contraction coupling, one being inhibition of calcium sequestration by the sarcoplasmic reticulum, the other a direct effect on the cell membrane leading to increased calcium entry.[30] Either of these effects could cause disturbances in myocardial conduction pathways leading to arrhythmias.

It is possible that aminophylline exerts its effects on cardiac muscle partly due to its release of cardiac catecholamines and in part by inhibition of phosphodiesterase and enhancement of the cyclic AMP system.[31] Cyclic AMP may be responsible for the effects of theophylline acting either in parallel with calcium or indirectly by mobilizing intracellular, bound calcium.[28] Halothane has been reported to cause effects compatible with the activation of adenyl cyclase and cyclic AMP.[32] Therefore, it could theoretically potentiate the arrhythmogenic effects of aminophylline by the same metabolic pathway.

The present study yields information about the arrhythmogenic effects of aminophylline in three different experimental settings; part 1, shortly (15 minutes) after induction of 1% halothane anesthesia, when aminophylline was administered in supratherapeutic amounts (50 mg/kg) by slow (5 minutes) intravenous infusion; part 2, after 2 hours of 1% halothane anesthesia, when aminophylline was administered in therapeutic amounts (10 mg/kg) by slow (5 minutes) intravenous infusion; and part 3, after prolonged (6 hours) 1% halothane anesthesia, when aminophylline was given in supratherapeutic amounts (25 mg/kg) by rapid (30 second) intravenous infusion to dogs that had low residual serum theophylline levels (5 to 10 mg/L) from part 2.

Previous studies in dogs have dealt with the effects of aminophylline administered shortly after initiation of halothane anesthesia.[5-7] In these studies aminophylline was administered 10, 15, and 30 minutes, respectively, following initiation of 1% halothane anesthesia. Doses of aminophylline varied from 6.4 to 50 mg/kg, but in all three studies severe, persistent ventricular arrhythmias (ventricular tachycardia or fibrillation) occurred in more than 50% of the experimental animals. These results differ markedly from that portion of our study (part 1) intentionally performed under similar conditions in an effort to duplicate these results. We saw no ventricular tachycardia or fibrillation at any time, and in only one of six animals did arrhythmia (bigeminy) persist as long as 19 minutes (Table 1). We did however, observe tachycardia and hypotension after aminophylline administration, as reported previously during halothane administration,[5] in all animals (Table 1), although no difference was apparent between animals developing arrhythmias and those which did not.

In serum ionized calcium, we saw no differences or changes which could be related to the presence or absence of arrhythmias (Table 2). Calcium concentrations remained relatively stable as arrhythmias occurred and resolved. Thus, any changes in myocardial calcium entry, which may have contributed to the genesis of arrhythmias, were either too small or too transient for us to detect with intermittent arterial blood sampling. There was no evidence of hypoxemia, hypercarbia, or acidosis (Table 2). Thus, these factors can be eliminated as possible precipitants of the arrhythmias which occurred.

The fact that no arrhythmias were observed in part 2 of our study, which involved achieving serum theophylline levels of approximately 20 mg/L by administration of aminophylline, 10 mg/kg, after 2 hours of 1% halothane anesthesia, agrees with the known lack of arrhythmogenic side effects at these serum theophylline levels in conscious humans.[12] There was no evidence of hypoxemia, hypercarbia, or acidosis before or after aminophylline administration (Table 3). Thus, the lack of arrhythmogenic activity would seem to indicate that halothane does not predispose to arrhythmias when therapeutic aminophylline dose levels are not exceeded in well ventilated animals.

Cardiotoxicity manifested by arrhythmias commonly occurs at serum theophylline levels between 20 and 40 mg/L in conscious humans.[12] One study of aminophylline toxicity in man concluded "... it is clear from the data that at least one-half the patients with plasma concentrations greater than 35 mg/L experienced a life-threatening arrhythmia."[33]

This is in accord with the results of part 3 of our study, which documented the arrhythmogenic effects of supratherapeutic blood levels (36 to 72 mg/L) of theophylline attained by administering aminophylline 25 mg/kg after 6 hours of 1% halothane anesthesia. Six of eight of these animals (75%) developed arrhythmias, although none had developed arrhythmias 4 hours previously when given aminophylline, 10 mg/kg. All six animals developed arrhythmias within 5 minutes of completion of the aminophylline infusion. Increases in in vivo phosphorylase enzyme activity within minutes of aminophylline administration have been reported,[34] and could be a factor in the genesis of the arrhythmias observed. Four of the six had ventricular disturbances (PVCs), yet in no case did the arrhythmia progress to ventricular tachycardia or fibrillation, as reported by others.[5-7] Instead, all ventricular arrhythmias reverted spontaneously to sinus rhythm within 2 minutes, and ventricular arrhythmias did not recur.

The results of our study, performed with all animals receiving 1% halothane anesthesia, may be summarized as follows: (1) Arrhythmias did not occur at therapeutic serum theophylline levels (10 to 20 mg/L) after prolonged (2 hours) halothane anesthesia. (2) Arrhythmias occurred in 63% (nine of 14) of the animals when high serum theophylline levels (above 36 mg/L) were present. (3) Ventricular arrhythmias occurred at high theophylline levels (above 36 mg/L) in 33% of the animals exposed to 15 minutes of halothane and in 50% of the animals exposed to 6 hours of halothane. (4) Ventricular arrhythmias occurred at high theophylline levels (above 36 mg/L) whether the aminophylline was given rapidly (30 seconds) or slowly (5 minutes). (5) Ventricular arrhythmias which began within 5 minutes of aminophylline administration at high theophylline levels (above 36 mg/L) always resolved spontaneously within 2 minutes of onset (eight of eight animals). Although the relationship between aminophylline, halothane, and ventricular vulnerability in man can only be inferential as a result of the studies performed here, our findings might serve as a helpful preliminary guide to the use of aminophylline during halothane anesthesia in the clinical setting.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the expert technical assistance of Steven D. Roe, Aleece E. Townsend, and Brad L. Whizin, and the secretarial skill of Patricia A. Herberg.

## REFERENCES

1. Hermann G, Aynesworth MB, Martin J: Successful treatment of persistent extreme dyspnea: "status asthmaticus." J Lab Clin Med 23:135-148, 1937
2. Shnider SM, Papper EM: Anesthesia for the asthmatic patient. Anesthesiology 22:886-892, 1961
3. Gold MI, Helrich M: A study of the complications related to anesthesia in asthmatic patients. Anesth Analg 42:283-293, 1963

4. Gold MI: Anesthesia for the asthmatic patient. Anesth Analg 49:881–888, 1970
5. Takaori M, Loehning RW: Ventricular arrhythmias during halothane anaesthesia: effect of isoproterenol, aminophylline, and ephedrine. Can Anaesth Soc J 12:275–280, 1965
6. Takaori M, Loehning RW: Ventricular arrhythmias induced by aminophylline during halothane anesthesia in dogs. Can Anaesth Soc J 14:79–86, 1967
7. Sharma PL: Effect of some adrenergic receptor antagonists on aminophylline-induced ventricular arrhythmias in dogs anaesthetized with halothane in oxygen. Indian J Med Res 57: 883–892, 1969
8. Barton MD: Anesthetic problems with aspirin-intolerant patients. Anesth Analg 54:376–380, 1975
9. Roizen MF, Stevens WC: Multiform ventricular tachycardia due to the interaction of aminophylline and halothane. Anesth Analg 57:738–741, 1978
10. Zimmerman BL: Arrhythmogenicity of theophylline and halothane used in combination. Anesth Analg 58:259–260, 1979
11. Mitenko PA, Ogilvie RI: Rational intravenous doses of theophylline. N Engl J Med 289:600–603, 1973
12. Piafsky KM, Ogilvie RI: Dosage of theophylline in bronchial asthma. N Engl J Med 292:1218–1222, 1975
13. Stirt JA, Berger JM, Ricker SM, et al: Aminophylline pharmacokinetics and cardiorespiratory effects during halothane anesthesia in experimental animals. Anesth Analg 59:186–191, 1980
14. Gushaw JB, Hu MW, Singh P, et al: Homogenous enzyme immunoassay for theophylline in serum. Clin Chem 23:1144, 1977
15. Han J, Moe GK: Nonuniform recovery of excitability in ventricular muscle. Circ Res 14:44–60, 1964
16. Han J, Garcia de Jalon P, Moe GK: Adrenergic effects on ventricular vulnerability. Circ Res 14:516–524, 1964
17. Katz RL, Bigger JT: Cardiac arrhythmias during anesthesia and operation. Anesthesiology 33:193–213, 1970
18. Hall KH, Norris FH: Fluothane sensitization of dog heart to action of epinephrine. Anesthesiology 19:631–641, 1953
19. Atuk NO, Blaydes MC, Westervelt FB, et al: Effect of aminophylline on urinary excretion of ephinephrine and norepinephrine in man. Circulation 35:745–753, 1967
20. Poisner AM: Direct stimulant effect of aminophylline on catecholamine release from the adrenal medulla. Biochem Pharmacol 22:469–476, 1973
21. Peach MJ: Stimulation of release of adrenal catecholamine by adenosine 3′-5′-cyclic monophosphate and theophylline in the absence of extracellular $Ca^{2+}$. Proc Natl Acad Sci USA 69:834–836, 1972
22. Snider SR, Waldeck B: Increased synthesis of adrenomedullary catecholamines induced by caffeine and theophylline. Naunyn Schmiedebergs Arch Pharmacol 281:257–260, 1974
23. Westfall DP, Fleming WW: Sensitivity changes in the dog heart to norepinephrine, calcium, and aminophylline resulting from pretreatment with reserpine. J Pharmacol Exp Ther 159: 98–106, 1968
24. Horowitz LN, Spear JF, Moore EN, et al: Effects of aminophylline on the threshold for initiating ventricular fibrillation during respiratory failure. Am J Cardiol 35:376–379, 1975
25. Butcher RW, Sutherland EW: Adenosine 3′,5′-phosphate in biological materials. I. Purification and properties of cyclic 3,5′-nucleotide phosphodiesterase and use of this enzyme to characterize 3′,5′-phosphate in human urine. J Biol Chem 237:1244–1250, 1962
26. Ueda I, Loehning RW, Ueyama H: Relationship between sympathomimetic amines and methylxanthines inducing cardiac arrhythmias. Anesthesiology 22:926–932, 1961
27. Tsien RW: Mode of action of chronotropic agents in cardiac Purkinje fibers. J Gen Physiol 64:320–342, 1974
28. Wooten GF, Thoa NB, Kopin IJ, et al: Enhanced release of dopamine $\beta$-hydroxylase and norepinephrine from sympathetic nerves by dibutyryl cyclic adenosine 3′-5′-monophosphate and theophylline. Mol Pharmacol 9:178–183, 1973
29. Belleman P, Scholz H: Relationship between theophylline uptake and inotropic effect in the guinea-pig heart. Br J Pharmacol 52:265–274, 1974
30. Blinks JR, Olson CB, Jewell BR, et al: Influence of caffeine and other methylxanthines on mechanical properties of isolated mammalian heart muscle. Circ Res 30:367–392, 1972
31. Marcus ML, Skelton CL, Grauer LE, et al: Effects of theophylline on myocardial mechanics. Am J Physiol 222:1361–1365, 1972
32. Bennis J, Smith U: Studies of the dual effects of halothane on the lipolysis of human fat cells. Anesthesiology 45:379–384, 1976
33. Hendeles L, Bighley L, Richardson RH, et al: Frequent toxicity from IV aminophylline infusions in critically ill patients. Drug Intell Clin Pharm 11:12–18, 1977
34. McNeill JH: Potentiation of norepinephrine-induced activation of cardiac phosphorylase by theophylline and reserpine. Can J Physiol Pharmacol 48:149–151, 1970

ANESTH ANALG
59:417-420, 1980

# Reduction of Enflurane-Induced Spike Activity by Scopolamine

S. S. Moorthy, MD,* R. V. Reddy, MD,† Raymond R. Paradise, PhD,‡
Alvin M. Losasso, MD,§ and Philip S. Gibbs, MD*

---

MOORTHY, S. S., REDDY, R. V., PARADISE, R. R., LOSASSO, A. M., AND GIBBS, P. S.: Reduction of enflurane-induced spike activity by scopolamine. Anesth Analg 59:417–420, 1980.

The possibility of enflurane-induced spike activity being related to a cholinergic mechanism was investigated. Thirty mongrel dogs were anesthetized with an inspired enflurane concentration of 3.5 ± 0.09% (mean ± SD) to obtain a sustained EEG spike activity. Scopolamine, in 0.04 mg/kg to 0.4 mg/kg IV doses, significantly decreased the spike activity ($p < 0.05$). We speculate that a central cholinergic muscarinic mechanism is at least partly responsible for the EEG spike activity produced by enflurane.

**Key Words:** ANESTHETICS, Intravenous: enflurane; BRAIN: electroencephalography; PARASYMPATHETIC NERVOUS SYSTEM: scopolamine; ACETYLCHOLINE: brain.

---

ENFLURANE produces electroencephalogram (EEG) spike activity,[1] and, at times, abnormal movements or even convulsions in humans characterized by high voltage spikes (150 to 200 $\mu$V) intermixed with an 8 to 10 Hz pattern.[2] EEG spike activity and associated muscular movements increase with an increase in inspired enflurane concentration and with a decrease in $Pa_{CO_2}$.[3]

Seizure activity is a multitransmitter phenomenon; acetylcholine and glutamate are excitatory, and thus facilitate seizures; norepinephrine and gamma aminobutyric acid are inhibitory and diminish seizure susceptibility.[4] Acetylcholine is an important component of seizure activity. For example seizures associated with brain trauma, epilepsy, electroconvulsive shock or pentylenetetrazole, brain acetylcholine, and cerebrospinal fluid (CSF) choline levels increase during the seizures indicating activation of the cholinergic system.[5] Postictally, following electroconvulsive therapy, a decrease in brain acetylcholine levels occurs in association with an increase in acetylcholine turnover in the brain and CSF.[5]

Further evidence implicating a central cholinergic component in the mechanism of seizure activity involves use of anticholinergic drugs such as atropine and scopolamine. Both of these drugs are capable of blocking seizures produced by exogenous acetylcholine and cholinesterase inhibitors.[6] Grob et al[7] have shown in man that intravenous atropine, 1.2 mg, inhibits the increased electrical activity of the brain produced by di-isopropyl flurophosphate. These investigators also observed that 1.2 mg of atropine reduces abnormal discharges and amplitude of the EEG in patients with a history of grand mal epilepsy displaying characteristic EEG changes.[7] Spontaneous and hyperventilation-induced petit mal EEG paroxysms are at times blocked by atropine.[8] The effects of anticholinergic drugs appear to relate to inhibition of the action of acetylcholine.

This study explores the possibility of a cholinergic component being involved in the mechanism of enflurane-induced seizure activity by evaluating the effect of scopolamine on enflurane-induced spike activity.

---

* Assistant Professor, Department of Anesthesiology.
† Assistant Professor, Department of Neurology.
‡ Professor, Departments of Anesthesiology and Pharmacology.
§ Professor, Department of Anesthesiology.

Financial assistance received from Ohio Medical Products.
Received from the Department of Anesthesiology, Indiana University School of Medicine, 1100 West Michigan Street, Indianapolis, Indiana 46223. Accepted for publication February 25, 1980. Presented at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, 1977.
Reprint requests to Dr. Moorthy.

## Methods and Materials

Mongrel dogs (7.8 ± 2.2 kg, mean ± SD) were anesthetized with enflurane in oxygen. Following tracheal intubation, ventilation was controlled, and intravenous and femoral arterial catheters were placed. Two subcutaneous frontal, two parietal, and a central reference electrode were placed. Esophageal temperature was maintained at 36 ± 1 C utilizing a heating blanket. A continuous infusion of 0.1% succinylcholine was used to prevent muscle twitching.

The inspired enflurane concentration was increased until spike activity was observed on the EEG. After spike activity was established the inspired enflurane concentration was thereafter maintained constant for at least 30 minutes. Dogs were divided into the following six groups: intravenous saline, 3 ml, was given to 12 control dogs; intravenous scopolamine, 0.01 mg/kg, was given to 4 dogs, 0.04 mg/kg to 8 dogs, 0.1 mg/kg to 4 dogs, 0.2 mg/kg to 7 dogs, and 0.4 mg/kg to 7 dogs. The number of spike waves (greater than 150 μV) was counted over a 30-second period before and 5, 10, 15, and 30 minutes after the drug administration. The average number of spikes per second was calculated and ranged from 0.7 to 2.8 in individual saline control experiments. The spike counting was done in triplicate with standard deviations of triplicate counts ranging from ±0 to ±8% of the triplicate mean. Data on dose-dependent effects of scopolamine were analyzed using the multiple comparison procedure to compare the effect of different doses of scopolamine with responses observed in saline control animals (Dunnett's test).[9] The extent of spike suppression by scopolamine at various time intervals was analyzed by two-way analysis of variance without interaction[10] and by the Tukey test.[11]

## Results

Spike activity was achieved and maintained for 30 minutes when the inspired enflurance concentration was 3.5 ± 0.09% ($p < 0.05$) at a time when $Pa_{CO_2}$ was 34 ± 4 torr. Scopolamine significantly ($p < 0.05$) decreased the number of spikes per second below corresponding values in saline control dogs significantly ($p < 0.05$) at doses of 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg at 5, 10, 15, and 30 minutes (Figs 1 and 2). After 0.01 mg/kg and 0.04 mg/kg of scopolamine, spike activity which was not significantly affected 5 minutes after injection, was significantly less 10, 15, and 30 minutes after injection. There were no significant differences in the extent of spike suppression induced by any of the doses of scopolamine used at the various time intervals. Mean arterial pressure and heart rate did not change significantly with scopolamine.

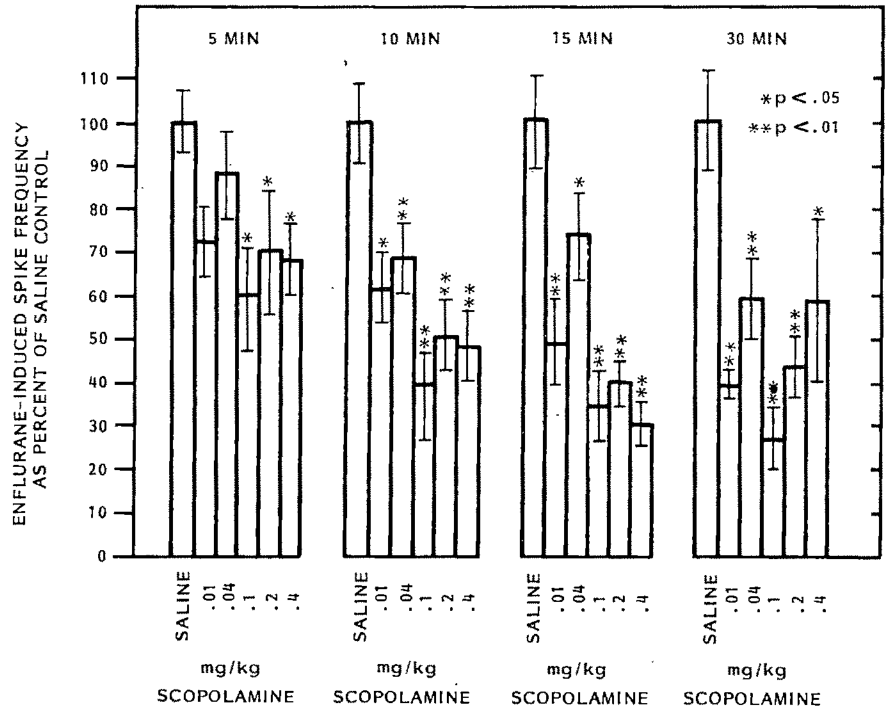


FIG 1. Effects of scopolamine on enflurane-induced spike frequency as compared to saline controls.

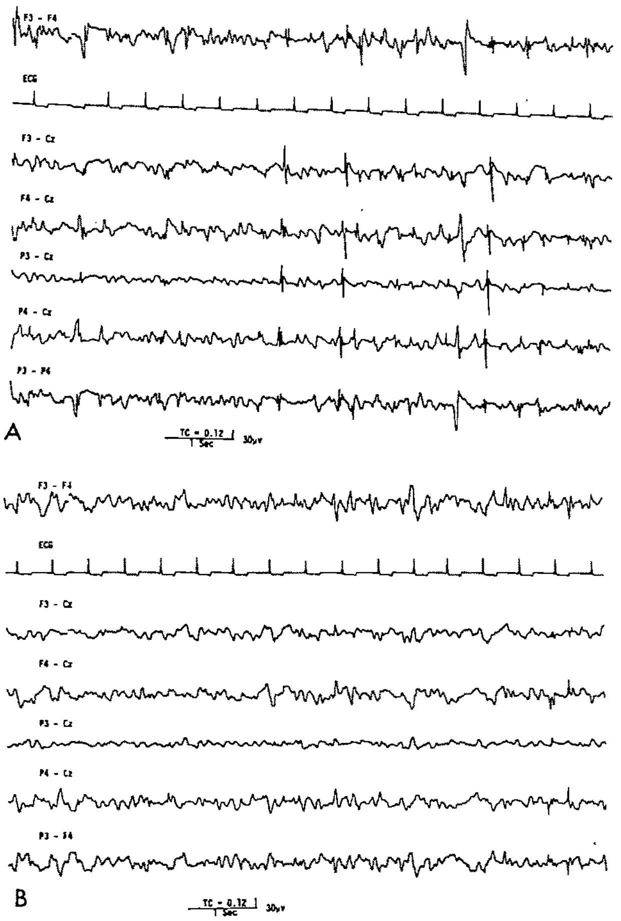


FIG 2. A, EEG showing spike activity induced with enflurane (inspired concentration 3.5%) and a $Pa_{CO_2}$ of 36 torr. The spike frequency was continuous over 30 minutes. B, Five minutes following intravenous scopolamine (0.2 mg/kg) in this dog (A) a decrease in spikes can be seen. This pattern continued over the next 30 minutes.

## Discussion

The central cholinergic system has both nicotinic and muscarinic cholinoceptive neurons. Spinal Renshaw cells are nicotinic,[12] whereas some cortical cells are muscarinic[13] and ventrothalamic neurons are of an intermediate type.[14] High concentrations of acetylcholine are found in the brain stem, caudate nucleus, and to some extent the pons, medulla, and cerebral cortex.[15] The central muscarinic effects of acetylcholine are blocked by even small doses of atropine or scopolamine.[6] Anticholinesterases such as organophosphorus and carbamates induce seizures or lower the threshold for strychnine or pentylenetetrazol-induced convulsions.[5] Seizures produced by anticholinesterases are due to high concentrations of free acetylcholine.[5]

The effects of anticholinergic drugs on cerebral electrical activity support the hypothesis that acetylcholine plays a role in normal cerebral cortical electrogenesis as well as electrogenesis associated with seizure activity. Atropine, for example, abolishes EEG activation produced by acetylcholine, arecoline, tremorine, and pilocarpine. The EEG synchronization produced by atropine and scopolamine can be abolished by eserine and, conversely, eserine-induced desynchronization can be antagonized by atropine. The EEG and motor seizures produced by high doses of cholinesterase inhibitors such as diisopropylfluorophosphate and sarin can be terminated by intravenous administration of atropine.[6]

Little has been published concerning the possible interaction of enflurane with the cholinergic muscarinic system of the brain. Ngai et al[16] have demonstrated in rat brain that while enflurane does not affect the acetylcholine turnover rate in subcortical structures, it does decrease the turnover rate of acetylcholine in the cerebral cortex. Halothane, on the other hand, decreases the turnover rate of acetylcholine in all parts of the brain.

The reduction in enflurane-induced intermittent spike activity by scopolamine reported in this paper suggests that cholinergic muscarinic receptors may be involved in the initiation of this spike activity. Since spike activity is preliminary to frank convulsive patterns as the concentration of enflurane increases, it is tempting to suggest that enflurane-induced seizures also involve muscarinic receptors. Our study, however, does not present direct information to support this view.

In addition to the anticholinergic action of scopolamine other possible actions of this drug should be considered in attempting to explain the mechanism by which scopolamine reduces enflurane-induced spike activity. The known CNS depressant action of scopolamine could be responsible for its effect on spike activity; however, there are two reasons why this possibility appears unlikely. An intravenous dose of 0.1 mg/kg of scopolamine does not significantly affect enflurane MAC in dogs (1.66 ± 0.12 vol% before scopolamine, 1.60 ± 0.15 vol% after scopolamine (R. R. Paradise, S. F. Dierdorf, and T. M. Wolfe: Unpublished data). Second, other CNS depressants such as barbiturates and diazepam do not attenuate the EEG changes induced by enflurane but in fact accentuate them.[17] Barbiturates produce synchronization of the EEG and markedly depress the evoked responses from the reticular activating system, whereas, atropine and scopolamine do not influence the reticular potentials evoked by applying single shocks to peripheral nerves.[18]

Enflurane-induced spike activity appears to be related more to minor motor seizures than to grand mal or other types of seizures.[17] In man barbiturates have a detrimental effect on minor motor seizures in contrast to their beneficial effects in grand mal activity.[19, 20] Both barbiturates in subanesthetic and anesthetic doses as well as diazepam augment enflurane-induced EEG changes in experimental animals.[17]

The lack of a dose-response effect of scopolamine on enflurane-induced spike activity may reflect a basic insensitivity of our methodology to detect small differences. Another possibility also seems likely: muscarinic cholinergic receptors might represent only one of several factors contributing to enflurane-induced spike activity. These other factors may be unrelated to the balance between scopolamine and CNS levels of acetylcholine.

Although it is difficult to draw conclusions by extrapolating our observations to man, it is possible that centrally acting anticholinergic drugs given as premedicants may reduce enflurance-induced spike activity. Further studies in man are necessary to confirm this speculation.

## ACKNOWLEDGMENTS

We are grateful to Dr. Robert K. Stoelting, Professor and Chairman, Department of Anesthesia, for his suggestions. We thank Ms. Sue Baldwin for technical help and Ms. Linda Hicks for secretarial help.

## REFERENCES

1. Lebowitz MH, Blitt CD, Dillon JB: Clinical investigation of compound 347 (Ethrane). Anesth Analg 49:1–10, 1970
2. Bart AJ, Homi J, Linde HW: Changes in power spectra of electroencephalograms during anesthesia with fluroxene, methoxyflurane and Ethrane. Anesth Analg 50:53–63, 1971
3. Lebowitz MH, Blitt CD, Dillon JB: Enflurane induced central nervous system excitation and its relation to carbon dioxide tension. Anesth Analg 51:355–363, 1972
4. Maynert EW, Marczynski TJ, Browning RA: The role of neurotransmitters in the epilepsies. Adv Neurol 13:79–147, 1975
5. Karczmar AG: Brain acetylcholine and seizures, in Psychobiology of Convulsive Therapy. Edited by M Fink, S Kety, J McGaugh, et al. Washington, DC, VH Winston & Sons, 1974, pp 251–270
6. Longo VG: Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacol Rev 18:965–996, 1966
7. Grob D, Harvey AM, Langworthy OR, et al: The administration of di-isopropyl flurophosphate (DFP) to man. III. Effect on central nervous system with special reference to the electrical activity of the brain. Johns Hopkins Hosp Bull 81:257–266, 1947
8. Toman JEP, Davis JP: The effects of drugs upon the electrical activity of brain. Pharmacol Rev 1:425–492, 1949
9. Dunnett CW: A multiple comparison procedure for comparing several treatments with a control. J Am Statistical Assoc 50: 1096–1121, 1955
10. Freund JE: Modern Elementary Statistics. Englewood Cliffs, NJ, Prentice-Hall, 1973, pp 349–352
11. Spence JT, Cotton JW, Underwood BJ, et al.: Elementary Statistics. Englewood Cliffs, NJ, Prentice-Hall, 1976, pp 195–198
12. Curtis DR, Phillis JW, Watkins JC: Cholinergic and noncholinergic transmission in the mammalian spinal cord. J. Physiol 158:296–323, 1961
13. Krnjevic K, Phillis JW: Pharmacological properties of acetylcholine-sensitive cells in the cerebral cortex. J Physiol 166:328–350, 1963
14. Andersen P, Curtis DR: The pharmacology of the synaptic and acetylcholine-induced excitation of ventrobasal thalamic neurones. Acta Physiol Scand 61:100–120, 1964
15. Pradhan SN, Dutta SN: Central cholinergic mechanism and behavior. Int Rev Neurobiol 14:173–231, 1971
16. Ngai SH, Cheney DL, Finck AD: Acetylcholine concentrations and turnover in rat brain structures during anesthesia with halothane, enflurane and ketamine. Anesthesiology 48:4–10, 1978
17. Darimont PC, Jenkins LC: The influence of intravenous anaesthetics on enflurane-induced central nervous system seizure activity. Can Anaesth Soc J 24:42–55, 1977
18. White RP, Sewell HA Jr, Rudolph AS: Drug induced dissociation between evoked reticular potentials and the EEG. Electroencephalogr Clin Neurophysiol 19:16–24, 1965
19. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics. Fifth edition. New York, Macmillan, 1975, p 222
20. Gumpert J, Paul R: Activation of the electroencephalogram with intravenous Brevital (methohexitone): the findings in 100 cases. J Neurol Neurosurg Psychiatry 34:646, 1971

ANESTH ANALG
59:421-425, 1980

# Developmental Toxicity of Methoxyflurane in Mice

**Robert S. Wharton, MD,* Timothy S. Sievenpiper, MD,† and Richard I. Mazze, MD‡**

---

WHARTON, R. S., SIEVENPIPER, T. S., AND MAZZE, R. I.: Developmental toxicity of methoxyflurane in mice. Anesth Analg 59:421–425, 1980.

The developmental toxicity of trace, subanesthetic, and anesthetic exposure to methoxyflurane was examined in Swiss/ICR mice. No adverse effects on reproduction or fetal development were demonstrated following exposure to trace (2 ppm) and subanesthetic (60 ppm) concentrations of methoxyflurane for 4 hours daily on days 6 through 15 of pregnancy. Exposure to an anesthetic concentration (2000 ppm; 0.2%) for the same period resulted in decreased fetal weight, decreased ossification, and delayed renal maturation. Additionally, the incidence of minor skeletal anomalies was increased. It is concluded that gestational exposure of mice to trace of subanesthetic concentrations of methoxyflurane does not result in reproductive loss or morphologic abnormalities in their offspring.

**Key Words:** ANESTHETICS, Volatile: methoxyflurane; PREGNANCY: fetal development; TOXICITY: methoxyflurane.

---

EXPOSURE to trace concentrations of anesthetic agents has been suggested as a cause of increased reproductive loss among operating room workers as well as increased rates of congenital malformation among their offspring.[1-3] Certain anesthetic agents, notably nitrous oxide and halothane, have been repeatedly investigated as potential teratogens.[4-10] However, the effects of methoxyflurane on reproduction and fetal development have not been adequately studied. The present study examines the developmental toxicity of gestational exposure to trace, subanesthetic, and anesthetic concentrations of methoxyflurane.

## Methods and Materials

Seven-week-old virgin male and female Swiss/ICR mice (Hilltop Lab Animals, Inc, Scottsdale, Pa) were marked with metal ear tags and allowed to acclimatize to the animal facility for two weeks. Mice were caged by sex, four animals per cage, and bedded on ground corncob (Tab Litter, Paxton Processing Co, Paxton, IL). Room temperature was maintained at 21 ± 1 C and artificial light was provided from 6 a.m. to 7 p.m. each day. No other animal species or mouse strains were housed in the same room and no germacides or pesticides were used. Food (Wayne LabBlox, Allied Mills, Inc, Chicago, IL) and water were available at all times except during treatment periods. Mice were weighed weekly. Females were recaged in pairs at 9 weeks of age. Each pair was mated nightly to one male until copulation occurred, or for a maximum of seven nights. The date of copulation was determined by the presence of a vaginal plug and was considered day 0 of pregnancy. Females that did not copulate in seven nights were mated for an additional seven nights with a different male. Pairs of females with the same day of copulation were recaged together and were assigned to one of five treatment groups (Table 1). Colony controls, group 1, were left undisturbed in

---

* Assistant Professor of Anesthesiology.

† Assistant Professor of Anesthesiology, State University of New York, Buffalo, New York.

‡ Professor of Anesthesiology.

Supported by the Veterans Administration Medical Center, Palo Alto, California.

Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305, and the Veterans Administration Medical Center, 3801 Miranda Avenue, Palo Alto, California 94304. Accepted for publication February 28, 1980. Presented, in part, at the 1978 Annual Meetings of the Teratology Society, Mackinac Island, Michigan, and the American Society of Anesthesiologists, San Francisco, California.

Reprint requests to Dr. Wharton, Anesthesiology Service (112A), VA Medical Center.

**TABLE 1**

**Exposure Schedule for Methoxyflurane Teratology Study**

| Group | Agent | Hours/day | Gestation days exposed | Comment |
|---|---|---|---|---|
| 1 | No treatment | — | — | Colony control |
| 2 | Compressed air | 4 | 6–15 | Treatment control |
| 3 | Methoxyflurane, 2 ppm | 4 | 6–15 | Trace exposure |
| 4 | Methoxyflurane, 60 ppm | 4 | 6–15 | Subanesthetic exposure |
| 5 | Methoxyflurane, 2000 ppm | 4 | 6–15 | Anesthetic exposure |

**TABLE 2**

**Classification of Fetal Abnormalities**

| External Abnormalities | Skeletal Abnormalities | Internal Abnormalities |
|---|---|---|
| Runt | Major malformations | Major malformations |
| Major malformations | Craniofacial | Minor anomalies |
| Cleft palate | Ribs or vertebrae | Enlarged brain ventricle |
| Exencephaly | Other | Hemorrhage |
| Limb deformity | Minor anomalies | Gonad displacement |
| Other | Ribs or vertebrae | Bladder distension |
| Minor anomalies | Sternebrae | Other |
| Hematoma | Other | Developmental variant |
| Limb malposition | Developmental variant | Increased renal pelvic cavitation |
| Crooked tail | Supernumerary rib | Other |
| Other | Asymmetric or bipartite sternum | |
| | Other | |
| | Decreased ossification | |
| | Skull | |
| | Limbs | |
| | Sternum | |
| | Other | |

the animal room and were untreated. Treatment controls, group 2, were exposed to compressed air only. Mice in groups 3, 4, and 5 were exposed to methoxyflurane, 2 ppm, 60 ppm, or 2000 ppm, respectively.

Inhalation exposures were carried out on days 6 through 15 of pregnancy and were of 4 hours duration. Exposures were performed in two stainless steel and Plexiglas, gas-tight chambers, each of approximately 1500-L capacity. The floor of the chambers was covered with soda lime to absorb carbon dioxide. Cages were placed randomly in the chambers. Methoxyflurane was vaporized in a copper kettle with medical grade compressed air delivered at a flow of 3 to 6 L/min. Uniform anesthetic vapor concentration was maintained in each chamber by a high volume recirculation fan. Methoxyflurane concentrations were monitored at 5- to 15-minute intervals using a Varian 1440 gas chromatograph, and were maintained within 10% of the desired concentrations.

Dams were sacrificed by cervical dislocation on day 18 of pregnancy, 1 day prior to the expected day of parturition. The uterus was examined and the number and position of live and dead fetuses and resorptions were recorded. Crown-rump length, weight, and sex of each live fetus were determined and each fetus was examined for external abnormalities. One third of the fetuses were fixed in Bouin's solution and subsequently examined for internal soft tissue abnormalities using a free-hand razor blade sectioning and microdissection technique.[11] The remaining two thirds were examined for skeletal abnormalities using a dissecting microscope. Skeletons were prepared by clearing the soft tissue with potassium hydroxide and staining the skeleton with alizarin red S, according to the method of Staples and Schnell.[12]

Abnormalities were classified by type and severity as follows (Table 2): Fetuses weighing 25% less than the litter mean were classified as runts; fetal morphologic abnormalities that would have precluded normal survival were considered major malformations, e.g., cleft palate or exencephaly; abnormalities that were neither severely disfiguring nor incapacitating were classified minor anomalies, e.g., crooked tail or wavy ribs; variations in normal development that were common in untreated animals were termed developmental variants, e.g., supernumerary ribs. Reduced ossification was classified separately from other skeletal variants since we wished to distinguish a process that only delayed fetal maturation from one that altered fetal morphology.

Mean weight gain, fetal length, fetal weight, number of implantations (total of live and dead fetuses plus resorptions), and live fetuses per litter were determined for all pregnant dams. Indices of reproductive loss, i.e., resorptions and fetuses dead in utero, equivalent to human abortions and stillbirths, respectively, were calculated for each female as percentages of the total number of implantations. The percentage of affected fetuses in each litter for each type of abnormality was computed. The means for each group were then determined. The litter was used as the basic experimental unit. Variables expected to have a normal distribution, i.e., weight, length, implantations, and live fetuses per litter, were analyzed by analysis of variance; the statistical significance of inter-group differences was determined by the Neuman-Keuls post-hoc test. Variables not expected to have a normal distribution, i.e., indices of reproductive loss and percentages of fetuses with morphologic abnormalities, were analyzed by the Mann-Whitney U test. The colony control and treatment control groups were compared with each other, and each methoxyflurane treatment group was compared with the treatment control group for that experiment; $p < 0.05$ was considered statistically significant.

## Results

Dams exposed to 2000 ppm of methoxyflurane became hyperactive, then slept during exposures and awakened approximately 15 minutes after exposures were terminated. The behavior of dams at the lowest two dosages was not affected by exposure. One dam exposed to 2000 ppm was found dead on the morning of day 7 of pregnancy; the cause of death could not be determined. Otherwise, there were no apparent adverse maternal effects associated with methoxyflurane exposure at any of the dosage levels studied. The overall pregnancy rates were similar in all five groups.

Examination of the reproductive indices (Table 3) failed to reveal any differences between colony control and treatment control groups except that there was a higher percentage of resorbed fetuses in the treatment controls (10.0 vs 5.0). However, in other studies from our laboratory,[9, 13] resorption rates among both colony and treatment control groups have averaged 10.0 ± 0.6%. Thus, the difference in resorption rates in the present study reflects a lower than normal rate in the colony controls, and it probably is a chance occurrence.

Methoxyflurane exposure did not affect dam weight gain, number of implantations and live fetuses per litter, percentage of fetuses resorbed, or overall reproductive loss (resorptions plus dead fetuses). Animals exposed to 2000 ppm had a higher percentage

**TABLE 3**

**Reproductive Indices following Methoxyflurane Exposure (mean ± SE)**

| | Colony control (group 1) | Treatment control (group 2) | Methoxyflurane | | |
|---|---|---|---|---|---|
| | | | 2 ppm (group 3) | 60 ppm (group 4) | 2000 ppm (group 5) |
| No. of females | 38 | 36 | 28 | 27 | 28 |
| Pregnancy rate (%) | 95 | 83 | 89 | 93 | 85 |
| Dam weight gain (g) | 26.0<br>±0.6 | 24.8<br>±0.6 | 24.1<br>±0.9 | 25.0<br>±0.7 | 22.4<br>±0.7 |
| Implantations/dam | 11.6<br>±0.3 | 12.2<br>±0.5 | 12.0<br>±0.4 | 12.5<br>±0.3 | 12.5<br>±0.4 |
| Live fetuses/litter | 10.9<br>±0.3 | 10.9<br>±0.5 | 10.1<br>±0.4 | 11.4<br>±0.4 | 11.3<br>±0.5 |
| Reproductive loss: | | | | | |
| Resorbed (%) | 5.0<br>±1.1* | 10.0<br>±1.6 | 15.1<br>±2.7 | 8.8<br>±2.1 | 7.9<br>±1.6 |
| Dead in utero (%) | 1.0<br>±0.5 | 0.0<br>±0.0 | 0.3<br>±0.3 | 0.7<br>±0.5 | 1.7<br>±1.0* |
| Mean fetal weight (g) | 1.36<br>±0.02 | 1.34<br>±0.03 | 1.33<br>±0.02 | 1.32<br>±0.03 | 1.02<br>±0.02* |
| Mean fetal length (mm) | 23.1<br>±0.1 | 22.8<br>±0.2 | 22.5<br>±0.2 | 22.5<br>±0.3 | 20.6<br>±0.2* |

* $p < 0.05$ vs treatment control.

**TABLE 4**

**Fetal Abnormalities following Methoxyflurane Exposure**

| | Colony control (group 1) | Treatment control (group 2) | Methoxyflurane | | |
|---|---|---|---|---|---|
| | | | 2 ppm (group 3) | 60 ppm (group 4) | 2000 ppm (group 5) |
| No. of litters | 36 | 30 | 25 | 25 | 23 |
| External examination | | | | | |
| No. of fetuses | 393 | 329 | 253 | 285 | 260 |
| Any external abnormality* | 2.3 | 2.4 | 3.0 | 0.9 | 2.7 |
| Runt | 1.1 | 0.8 | 2.6 | 0.3 | 1.6 |
| Major malformation | 0.0 | 1.1 | 0.4 | 0.3 | 0.3 |
| Minor anomaly | 1.2 | 0.5 | 0.4 | 0.3 | 0.7 |
| Skeletal examination | | | | | |
| No. of fetuses | 261 | 221 | 166 | 191 | 173 |
| Any skeletal abnormality* | 33.4 | 36.7 | 40.0 | 31.7 | 97.2† |
| Major malformation | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Minor anomaly | 1.7 | 1.1 | 1.1 | 2.5 | 14.0† |
| Developmental variant | 28.3 | 28.9 | 24.0 | 22.2 | 39.9 |
| Decreased ossification | 6.1 | 12.1 | 21.4 | 12.3 | 96.0† |
| Internal examination | | | | | |
| No. of fetuses | 132 | 108 | 87 | 94 | 87 |
| Any internal abnormality* | 30.0 | 34.8 | 55.8† | 31.9 | 61.0† |
| Major malformation | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Minor anomaly | 3.0† | 10.1 | 17.7 | 10.0 | 13.8 |
| Developmental variant/IRPC‡ | 29.3 | 27.9 | 45.8† | 26.9 | 57.8† |

* Mean percent of abnormal fetuses per litter.

† $p < 0.05$ vs treatment control.

‡ IRPC, Increased renal pelvic cavitation.

of fetuses dead in utero than did treatment controls. Mean weight and length of surviving fetuses were decreased, by 24% and 10%, respectively, in the high exposure group only.

The results of fetal morphologic examination are presented in Table 4. The percentage of minor anomalies found on internal examination was higher in treatment controls than in colony controls, although no specific type of anomaly predominated. Otherwise, the two control groups did not differ. At the 2-ppm exposure level, there was an increased incidence of developmental variants on internal examination, specifically, delayed renal maturation (increased renal pelvic cavitation). At 60 ppm, there were no significant adverse effects on fetal morphologic development. Fetuses from dams exposed to 2000 ppm, however, had a greatly increased incidence of minor skeletal abnormalities (i.e., bent, wavy, and fused ribs, and fused vertebrae), decreased ossification, and a greater incidence of increased renal pelvic cavitation.

## Discussion

In the present study, daily exposure of mice to trace (2 ppm) and subanesthetic (60 ppm) concentrations of methoxyflurane during the period of fetal organogenesis had no effect on fetal viability at term, mean fetal weight, or the incidence of major or minor developmental abnormalities. The only finding at the 2-ppm exposure, delayed renal pelvic maturation, was probably a chance occurrence, since a similar effect was not observed following exposure to 60 ppm and overall fetal development was not retarded. In contrast to the lack of effects at low-dose exposure, exposure to an anesthetic concentration (2000 ppm) resulted in marked developmental retardation and an increased incidence of minor morphologic anomalies. Overall reproductive loss (resorptions and dead fetuses) was not increased. The increased incidence of fetuses dead in utero following the 2000-ppm exposure is, in part, a result of the low incidence of fetal deaths in the treatment control group in this study; in other studies, the incidence of fetal deaths in control litters has ranged from 0.0% to 2.3% (reference 9 and R. Wharton, unpublished data).

It is of interest that all morphologic abnormalities involved the fetal skeleton, since fetal plasma levels of inorganic fluoride increase following methoxyflurane exposure,[14, 15] and fluoride has a high affinity for fetal bone.[16] However, the developing skeleton frequently is more sensitive than other organ systems to the effects of teratogenic agents and may be the only organ affected.[17] Thus, the abnormalities seen in the present study are not necessarily related to methoxyflurane metabolism to inorganic fluoride.

The results of the present study are similar to those reported by Pope et al,[8] who examined methoxyflurane fetotoxicity in Sprague-Dawley rats exposed for 8 hours/day on days 1 to 21 gestation. Average fetal weight was decreased following exposure to 100, 400, and 800 ppm; the highest two doses also resulted in decreased fore-limb ossification, indicating retardation of fetal development. Neither reproductive loss nor the incidence of gross skeletal anomalies was increased. The observed effects were similar to those produced by exposure to comparable concentrations of halothane, nitrous oxide, or a halothane-nitrous oxide mixture.[8] Thus, with the exception of slight developmental retardation resulting from exposure to high subanesthetic concentrations, there is no evidence that gestational exposure to trace or subanesthetic exposure of methoxyflurane poses a reproductive hazard.

It is not known whether the effects observed at anesthetic concentrations in this study resulted from a direct toxic effect of methoxyflurane and/or its metabolites on developing embryonic tissue, or whether they were indirect effects resulting from maternal stress, impaired nutritional status, or general anesthesia-related physiologic alterations, such as hypotension, hypoventilation, metabolic depression, or decreased uterine blood flow. We believe these are indirect effects since similar defects have occurred following exposure to high subanesthetic and anesthetic concentrations of other agents.[4-10, 13] In a previous study[10] we demonstrated that gestational exposure of mice to subanesthetic concentrations of halothane was neither teratogenic nor embryolethal; however, exposure to an anesthetic concentration (1.0%) was lethal to 60% of pregnant females, and it was embryolethal or teratogenic in all litters of surviving dams.[10] Similarly, gestational exposure to enflurane, 1.0%, resulted in developmental retardation and increased incidences of cleft palate and lumbar ribs; exposure to lower concentrations had no detectable effect.[13] In other studies, nitrous oxide was found to be teratogenic and embryolethal in Sprague-Dawley rats when administered at concentrations of 50% to 70% for 24 hours or longer during midgestation.[4, 5, 18] Thus, all inhalational anesthetics in current use, when administered to pregnant animals at anesthetic or near-anesthetic concentrations for sufficient duration, can produce embryotoxic effects. The similarity of the embryotoxic effects suggests that they may be characteristic of all anesthetics and that they may occur by a common mechanism. Furthermore, the similar anesthetic potencies at which fetal effects are observed suggests that embryotoxicity may be closely related to anesthetic action. However, the fact that embryotoxic effects are produced at anesthetic or near-anesthetic drug concentrations cannot be used to infer that similar effects will follow exposure to trace or subanesthetic concentrations.

What relevance do these results have to humans? The mechanisms by which drugs may affect embryonic development, are similar in all mammalian species. Therefore, drugs that are embryotoxic in one species are frequently found to be embryotoxic in others, and those that are safe in several species are likely to be safe in others. However, species differences in sensitivity to teratogenic agents may exist, due to differences in maternal and fetal metabolism, placental function, and susceptibility of developing embryonic structures to toxic substances. Thus, this study demonstrating that gestational exposure to subanesthetic concentrations of methoxyflurane is neither teratogenic nor embryotoxic in mice is reassuring, but cannot provide absolute evidence of safety in man.

## REFERENCES

1. Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel, American Society of Anesthesiologists: Occupational disease among operating room personnel: a national study. Anesthesiology 41:321-340, 1974
2. Knill-Jones RP, Moir DB, Rodrigues LV, et al: Anaesthetic practice and pregnancy: controlled survey of women anesthetists in the United Kingdom. Lancet 1:1326-1328, 1972
3. Corbett TH, Cornell RG, Endres JL, et al: Birth defects among children of nurse anesthetists. Anesthesiology 41:341-344, 1974
4. Fink BR, Shepard TH, Blandau RJ: Teratogenic activity of nitrous oxide. Nature 214:146-148, 1979
5. Shepard TH, Fink BR: Teratogenic activity of nitrous oxide in rats, in Toxicity of Anesthetics. Edited by BR Fink. Baltimore, Williams & Wilkins Co, 1968, pp 308-323
6. Basford A, Fink BR: Teratogenicity of halothane in the rat. Anesthesiology 29:1167-1173, 1968
7. Lansdown ABG, Pope WDB, Halsey MJ, et al: Analysis of fetal development in rats following maternal exposure to subanesthetic concentrations of halothane. Teratology 13:299-304, 1976
8. Pope WDB, Halsey MJ, Lansdown ABG, et al: Fetotoxicity in rats following chronic exposure to halothane, nitrous oxide, or methoxyflurane. Anesthesiology 48:11-16, 1978
9. Wharton RS, Mazze RI, Baden JM, et al: Fertility, reproduction and postnatal survival in mice chronically exposed to halothane. Anesthesiology 48:167-174, 1978
10. Wharton RS, Wilson AI, Mazze RI, et al: Fetal morphology in mice exposed to halothane. Anesthesiology 51:532-537, 1979
11. Barrow MV, Taylor WJ: A rapid method for detecting malformations in rat fetuses. J. Morphol 127:291-306, 1969
12. Staples RE, Schnell VL: Refinements in rapid clearing technique in the KOH-alizarin red S method for fetal bone. Stain Technol 43:61-63, 1968
13. Wharton RS, Wilson AI, Rice SA, et al: Teratogenicity of enflurane in Swiss/ICR mice (abstract). Teratology 19:53A, 1979
14. Palahniuk RJ, Cumming M: Plasma fluoride levels following obstetrical use of methoxyflurane. Can Anaesth Soc J 22:291-297, 1975
15. Clark RB, Beard AG, Thompson DS, et al: Maternal and neonatal plasma inorganic fluoride levels after methoxyflurane analgesia for labor and delivery. Anesthesiology 45:88-91, 1976
16. Fiserova-Bergerova V: Fluoride in bone of rats anesthetized during gestation with enflurane or methoxyflurane. Anesthesiology 45:483-486, 1976
17. Kimmel CA, Wilson JG: Skeletal deviations in rats: Malformations or variations? Teratology 8:309-316, 1973
18. Lane GA, Nahrwold MD, Tait AR, et al: Nitrous oxide is teratogenic: xenon is not (abstract)! Anesthesiology 51:S260, 1979

ANESTH ANALG
59:426-430, 1980

# Effect of Halothane, Enflurane, and Nitrous Oxide on Tracheal Ciliary Activity in Vitro

**Kyu Sun Lee, MD,* and Sung Suh Park, MD†**

---

LEE, K. S., AND PARK, S. S.: Effect of halothane, enflurane, and nitrous oxide on tracheal ciliary activity in vitro. Anesth Analg 59:426-430, 1980.

Effects of halothane, enflurane, and nitrous oxide on ciliary beats were evaluated using a photoelectric system in dissected rabbit tracheal segments. Dose-dependent suppression of the frequency of ciliary beats of moderate degrees was observed after exposure of tracheal segments to warmed and humidified vapors of halothane and enflurane. No suppression, however, was noted after exposure to nitrous oxide. These findings suggest that halothane and enflurane directly suppress ciliary activity.

**Key Words:** LUNG: tracheal cilia; ANESTHETICS, Volatile: halothane; ANESTHETICS, Volatile: enflurane; ANESTHETICS, Gases: nitrous oxide.

---

PULMONARY atelectasis, pulmonary infection, as well as damage of the tracheal mucosa are recognized postoperative complications. These complications have been attributed in part to the disturbance or failure of mucociliary clearance. Maintenance of efficient ciliary activity throughout the respiratory tract is probably an important factor in the prevention of the accumulation of secretions and postoperative pulmonary complications.

Suppression of ciliary activity by inhalation anesthetics has long been recognized. In 1928 Hill[1] reported that ether and chloroform inhibited ciliary activity. Proetz,[2] however, attributed the ciliosuppressive effect of ether vapor to the cooling of the tracheal tissue by ether vapor rather than to a specific action of ether on the ciliary activity. In 1962, Rivera[3] stated that usual concentrations of nitrous oxide have no significant effect on ciliary activity. In 1974, Nunn et al[4] evaluated the ciliosuppressive effects of inhalation anesthetics in Tetrahymena pyriformis. They measured the speed of swimming produced by ciliary motion as an index of ciliary activity and found that six inhalation anesthetics (trichloroethylene, chloroform, methoxyflurane, halothane, diethyl ether, and cyclopropane) suppressed swimming speed at anesthetic concentrations. Recently, Forbes[5] and Patrick and Stirling[6] demonstrated ciliosuppressive effects of halothane in dogs and rats, respectively, by measuring movement of radioactive marker substances deposited on the trachea. Using a similar method, Forbes and Horrigan[7] further reported that dose-dependent suppression of mucus flow rate was produced by enflurane as well as by halothane. In additional studies by Forbes and Gamsu,[8,9] 1.2 MAC of halothane or diethyl ether suppressed clearance of tantalum deposited in the central and peripheral airways. Thiopental also suppressed tantalum clearance when it was used for a prolonged period at an equivalent anesthetic dose.[8]

---

* Instructor in Anesthesiology, Albert Einstein College of Medicine; Attending Anesthesiologist, Pelham Bay General Hospital, Bronx, New York.

† Associate Professor of Medicine, Albert Einstein College of Medicine.

Supported in part by National Institutes of Health grant HL 18308.

Received from the Albert Einstein College of Medicine, Departments of Medicine and Anesthesiology, 1300 Morris Park Ave, Bronx, New York 10461. Accepted for publication February 9, 1980. Presented at the Annual Meeting of the American Thoracic Society, Boston, 1978.

Reprint requests to Dr. Park. Pulmonary Division, Department of Medicine, Van Etten Hospital, Room 612, Pelham Parkway and Eastchester Rd., Bronx, NY 10461.

Recently, in our laboratory a method for direct measurement of ciliary beats in mammalian tracheal segments has been developed by modifying the method described by Dalham and Rylander.[10] Using this method, we studied the effects of halothane, enflurane, and nitrous oxide on the frequency of ciliary beats in rabbit tracheal segments.

## Methods

### Apparatus for Measurement of Ciliary Beats

The photocell method developed by Dalham and Rylander[10] and Rylander[11] was modified by the addition of a dissecting microscope-television camera monitoring system.[12] Fig. 1 shows the apparatus used for the study.

Incident light reflected on the surface of the cilia beating in waves generates microscopically visible oscillating light images. Through a television camera placed in the ocular tube of a 50-power dissecting microscope, the oscillating light image is transmitted to a television monitor. The angle and intensity of the light source can be varied so as to produce the sharpest image of the reflected light with a minimal background light intensity on the monitor screen. The final magnification by the microscope-television monitor system is × 140. The transmitted light signal is picked up by a photosensitive cadmium sulfide cell (Phillips ORP 61) placed directly over the image on the television monitor. The output from the photocell is fed into an amplifier which filters out the high frequency component (greater than 40 cycles per second) related to the oscillating electron beam of the monitor's picture tube, leaving only the lower frequency component related to the ciliary beat. The output from the amplifier is fed into an oscilloscope and recorded.

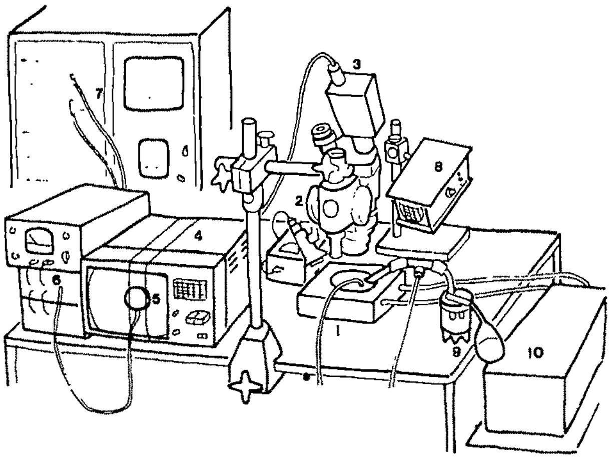


FIG 1. Apparatus used for the study. Main part of the apparatus consists of a temperature and humidity-controlled chamber (1) and a dissecting stereomicroscope (2) with a television camera (3) placed into one of the ocular tubes shown in the center. The photoelectric monitoring system consists of a television monitor (4) with a photocell (5) attached to the surface of the screen, an amplifier (6), and a recorder (7) shown on the left. Remaining apparatus shown on the right are an air curtain (8), hand nebulizer (9), and circulating water bath (10).

For in vitro observation of ciliary beats, a temperature- and humidity-controlled chamber was constructed. The chamber is made of transparent Plexiglas and has a round well (8 cm diameter, 2 cm deep) surrounded by a circulating temperature-controlled water jacket. The well is covered by a removable transparent plastic lid with an inlet tube for application of aerosolized or gaseous agents and an outlet hole for the exit of these agents.

Using a Bennett temperature-regulated humidifier connected to the anesthesia machine, the anesthetic gas mixtures were warmed and humidified before delivery into the exposure chamber. The temperature of the anesthetic gas mixture was monitored by a Tele-thermometer (Yellow Springs Instrument Co) at the inlet tube and was maintained equal to or slightly higher than that of the water circulating the exposure chamber (37 C). This precaution was necessary to prevent drying of the tracheal tissue. The flow rates of anesthetic gas mixtures averaged 8 L/min.

Condensation of water vapor on the inner surface of the covering lid was prevented by heating the lid to a temperature slightly above the circulating water temperature. This was conveniently achieved using the Air Curtain Incubator (Sage Instruments Division, Orion Research Inc, Cambridge, MA). This system senses and maintains the surface temperature of the lid by intermittently blowing heated air onto it.

### Protocol

Each rabbit was anesthetized by intravenous infusion of 15 mg of pentobarbital per kilogram of body weight. A 3- to 4-cm long section of trachea was removed and divided into four segments. One of the cut segments was immediately placed in a humidity- and temperature-controlled chamber. The remaining segments were wrapped with gauze moistened with physiologic saline and were kept in a Petri dish at room temperature to be used for later experiments. Ciliary beats were continuously monitored for about 30 minutes until they became stable. Warmed and humidified air-halothane vapor mixture was then introduced into the chamber, starting with 0% halothane and then increasing successively to 0.8%, 1.6%, 2.4%, and 3.2%. The 0.8% halothane corresponds to 1 MAC established in humans[13] and rabbits.[14] The period of exposure to each concentration of halothane was 8 to 10 minutes. Ciliary beats were recorded toward the end of each period. Observations were repeated using 14 tracheal segments obtained from four different rabbits. In a separate experiment, a single exposure to halothane at a concentration of 3.2% was carried out in six additional tracheal segments.

Using the same protocol, exposure to enflurane-air mixtures of successively increasing concentrations (0%, 1.6%, 3.2%, 4.8%, and 6.4%) was carried out in 15 tracheal segments. The 1.6% enflurane corresponds to 1 MAC established in human.[15] Exposure to nitrous oxide was similarly carried out in an additional ten tracheal segments using concentrations of 0%, 50% to 65%, 75%, and 80% to 90%. Oxygen was used as a background gas for nitrous oxide except for the control measurements which were carried out in room air.

To evaluate reversibility of ciliary suppression, groups consisting of four tracheal sections were separately exposed to four MAC concentrations of halothane or enflurane and then re-exposed to the warmed humidified air.

Calibration of the anesthetic vaporizer was carried out individually for each anesthetic agent used with the resulting concentrations monitored by gas chromatography (Perkin-Elmer).

Examples of records of the ciliary beats are shown in Fig. 2. Each oscillation corresponds to the fluctuation of intensity of the light reflected on the beating cilia. By counting the frequency of oscillations over a period of 1 second (five blocks) the number of ciliary beats was determined. At each concentration of anesthetics, five or more determinations of ciliary beats as mentioned above were obtained and the values were averaged.

### Reproducibility and Statistical Analysis

Reproducibility of the measurements was evaluated using three tracheal segments obtained from the same rabbit. Each segment was separately exposed over a 3-hour period in the warmed and humidified air and the ciliary beats were monitored at 8- to 10-minute intervals. In a given spot of the tracheal section, ciliary beats became stable within 30 minutes after the section was placed into the chamber and remained stable over the 3-hour period monitored. The coefficient of variation of ciliary beats was 3%.

Despite the good reproducibility of ciliary beat counting, there was a considerable variation in the control ciliary beats (14 to 24 beats per second) among the rabbits and also, to a lesser extent, among the tracheal sections from the same rabbit. Because of these variations of control values, all data of ciliary beats were expressed as percent of the control frequency of ciliary beats obtained in each tracheal section.

## Results

The effects of halothane, enflurane, and nitrous oxide on the frequency of ciliary beats are shown in Table 1. Whereas no ciliary suppression was noted after exposure to various concentrations of nitrous

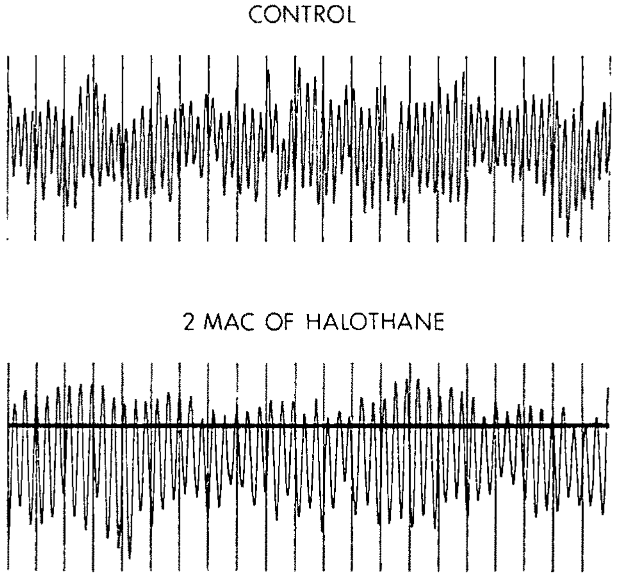


FIG 2. Record of ciliary beats. Each oscillating signal corresponds to the reflected light from a group of beating cilia. The time interval between the vertical lines is 0.2 second. (The heavy horizontal line in the lower panel represents a baseline for adjustment of the amplifier gain.)

**TABLE 1**

**Effects of Halothane, Enflurane and Nitrous Oxide on Frequency of Ciliary Beats***

| | | | | |
|---|---|---|---|---|
| Halothane concentration | 0.8% | 1.6% | 2.4% | 3.2%† |
| No of observations | 14 | 14 | 14 | 14 |
| Mean ± SE | 93 ± 1.6 | 83 ± 3.0 | 78 ± 3.8 | 75 ± 4.0 |
| Enflurane concentration | 1.6% | 3.2% | 4.8% | 6.4% |
| No of observations | 15 | 15 | 15 | 15 |
| Mean ± SE | 91 ± 3.6 | 80 ± 2.7 | 74 ± 2.6 | 70 ± 3.2 |
| Nitrous oxide concentration | 50–64% | 75% | 80% | 85–90% |
| No of observations | 10 | 10 | 13 | 10 |
| Mean ± SE | 99 ± 2 | 98 ± 2 | 100 ± 1 | 100 ± 3 |

* Values are means ± 1 SE of ciliary beats expressed as percent of control beat frequency.

† In six separate experiments in which the tracheal segments were exposed to 3.2% halothane in one step without prior exposure to lower concentrations of halothane mean value was 74 ± 2.9.

oxide, ranging from 50% up to 90%, increasing suppression of ciliary beat frequency was observed after exposure to successively increasing concentrations of halothane and enflurane. Ciliary suppression of similar degrees was observed at 3.2% halothane, whether this concentration was reached in one step from zero concentration or through steps of exposure to successively increasing concentrations of halothane.

Dose-response relationships for halothane and enflurane are shown in Fig 3. The frequencies of the ciliary beats are linearly related to log dose expressed in MAC. The correlation coefficient was 0.52 for halothane and 0.57 for enflurane; they are highly significant ($p < 0.01$). Although halothane showed slightly less steep slope and higher Y estimate at 2 MAC than enflurane, the differences were not statistically significant.

The results of experiments carried out to evaluate the reversibility of ciliary suppression are shown in Table 2. Both the halothane- and enflurane-induced ciliary suppression reverted to control values after reexposure to warmed and humidified air.

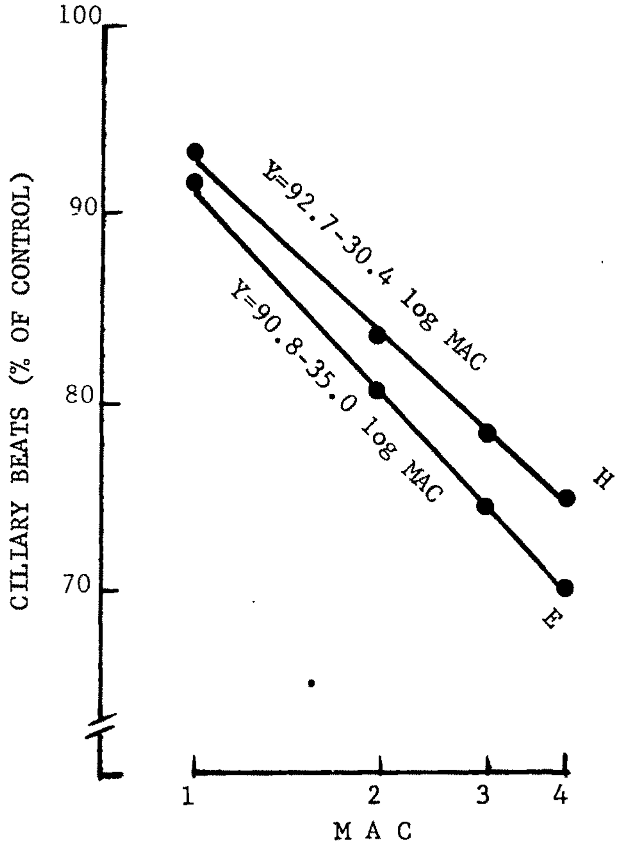


FIG 3. Effect of halothane and enflurane on ciliary beats. Each point represents the mean ciliary beats, in percent of control values, obtained at each MAC of halothane (H) or enflurane (E). Least square regression lines computed from the data are shown. The 95% confidence intervals of the slope and Y estimate at 2 MAC are, respectively, −30.4 ± 12.8 and 83.5 ± 2.9 for halothane and −35.0 ± 13.3 and 80.3 ± 3.0 for enflurane.

**TABLE 2**

**Reversibility of Ciliary Suppression by Halothane and Enflurane***

|  | Control | 4 MAC | Recovery |
|---|---|---|---|
| Halothane | 14.4 | 11.2 | 12.8 |
|  | 13.8 | 10.3 | 13.0 |
|  | 16.2 | 14.4 | 16.5 |
|  | 15.6 | 10.5 | 15.8 |
| Enflurane | 13.8 | 7.7 | 12.2 |
|  | 16.8 | 13.0 | 16.0 |
|  | 12.5 | 9.0 | 12.0 |
|  | 16.0 | 12.5 | 14.8 |

* Values are ciliary beats per second.

## Discussion

Clearance of marker substances deposited on the airways has been measured to assess the ciliosuppressive action of general anesthetics in vivo. Although this method has merit as an index of overall efficiency of mucociliary clearance, it lacks specificity as an index of ciliary activity. Besides the alteration in the ciliary activity, changes in the physical properties of mucus secretions also affect the efficiency of mucociliary clearance. As hypothesized by Lucus and Douglas[16] the mucociliary transport system is covered by a double layer consisting of a superficial viscid sheet of mucus and an underlying layer of serous fluid. The cilia beat in the serous fluid and interact with the mucus layer above, producing transport of mucus. Although the exact mechanisms are not known, the ciliary-mucus interaction has been considered an important factor determining the efficiency of the mucus flow. In support of this hypothesis, Sade et al[17] have shown that a dissected frog palate becomes depleted of its mucus layer soon after death and loses its capacity to transport particles deposited on it, even though the cilia continue to beat for a long time. We confirmed this in our rabbit tracheal sections. It is likely that the tracheal sections employed in our study were largely depleted of mucus by the time the ciliary beats were counted. In such a mucus-depleted preparation, little mucus-cilia interaction is expected to occur, and the decrease in the ciliary beats observed after exposure to halothane and enflurane may largely be attributed to a direct action of these agents on the mechanisms of ciliary activity.

The extent of suppression of ciliary beat frequency by halothane and enflurane was relatively mild and was linearly related to log dose. In contrast in vivo studies of halothane and enflurane by Forbes[5] and Forbes and Horrigan[7] showed more pronounced deceleration of mucus flow which was linearly related to arithmetic rather than log MAC concentrations. Because of the limited understanding of the mechanisms of cilia-mucus interaction, it is difficult to assess the implication of these findings. It is conceivable that different methods evaluate different aspects of the complex multiple regulatory mechanisms involved in the mucociliary clearance. It is not known whether halothane and enflurane have direct action on the mucus secretions. Such a direct action, should it exist, may contribute to the suppression of mucus flow rate in vivo, perhaps interacting with the direct ciliosuppressive effect of these agents.

Although the frequency of ciliary beats is an important part of the ciliary function, additional information regarding the forcefulness of ciliary beats is essential for full understanding of ciliary function. It may be speculated that a decrease in the frequency of beating may be associated with a concomitant decrease in the force of ciliary beats. Combination of these two factors may account for the pronounced impairment of the mucus flow rate mentioned above. Additional studies are required to understand the complex aspects of mucociliary clearance mechanisms.

In contrast to halothane and enflurane, nitrous oxide had no suppressive effect on the ciliary beats. The reason for the difference is not clear. It may be that, because of the low potency of the nitrous oxide, the concentration required for suppression may not have been reached under the experimental conditions employed.

## REFERENCES

1. Hill L: The ciliary movement of the trachea studied in vitro, a measure of toxicity. Lancet 215:802–805, 1928
2. Proetz AW: Essay on the Applied Physiology of the Nose. Second edition. St Louis, Annals Publishing Co, 1953
3. Rivera JA: Cilia, Ciliated Epithelium and Ciliary Activity. New York, Pergamon Press, 1962, p 71
4. Nunn JF, Sturrock JE, Wills EJ, et al: The effect of inhalation anaesthetics on the swimming velocity of Tetrahymena pyriformis. J Cell Sci 15:537–554, 1974
5. Forbes AR: Halothane depresses mucociliary flow in the trachea. Anesthesiology 45:59–63, 1976
6. Patrick G, Stirling C: Measurement of mucociliary clearance from the trachea of conscious and anesthetized rats. J Appl Physiol 42:451–455, 1977
7. Forbes AR, Horrigan RW: Mucociliary flow in the trachea during anesthesia with enflurane, ether, nitrous oxide and morphine. Anesthesiology 46:319–321, 1977
8. Forbes AR, Gamsu G: Mucociliary clearance in the canine lung during and after general anesthesia. Anesthesiology 50:26–29, 1979
9. Forbes AR, Gamsu G: Depression of lung mucociliary clearance by thiopental and halothane. Anesth Analg 58:387–389, 1979
10. Dalham T, Rylander R: Frequency of ciliary beat measured with a photosensitive cell. Nature 196:592–593, 1962
11. Rylander R: Current techniques to measure alterations in the ciliary activity of intact respiratory epithelium. Am Rev Respir Dis 93(suppl):67–73, 1966
12. Park SS, Kikkawa Y, Goldring IP, et al: An animal model of cigarette smoking in beagle dogs: correlative evaluation of effects on pulmonary function, defense and morphology. Am Rev Respir Dis 115:971–979, 1977
13. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 26:756–763, 1965
14. Davis NL, Nunnally RL, Malinin TI: Determination of the minimum alveolar concentration (MAC) of halothane in the white New Zealand rabbit. Br J Anaesth 47: 341–345, 1975
15. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. Anesthesiology 35:361–364, 1971
16. Lucas A, Douglas LC: Principles underlying ciliary activity in the respiratory tract. Arch Otolaryngol 20:518–541, 1934
17. Sade J, Eliezer N, Silberberg A, et al: The role of mucus in transport by cilia. Am Rev Respir Dis 102:48–52, 1970

ANESTH ANALG
59:431-434, 1980

# Glycopyrrolate-Neostigmine and Atropine-Neostigmine Mixtures Affect Postanesthetic Arousal Times Differently

**Anis Baraka, MD,* Jean-Pierre Yared, MD,† Anne-Marie Karam, MD,‡ and Alon Winnie, MD§**

---

BARAKA, A., YARED, J.-P., KARAM, A.-M., AND WINNIE, A.: Glycopyrrolate-neostigmine and atropine neostigmine mixtures affect postanesthetic arousal times differently. Anesth Analg 59:431-434, 1980.

Atropine-neostigmine and glycopyrrolate-neostigmine mixtures used in 54 premedicated patients for reversal of non-depolarizing neuromuscular blockade were compared for their effects on postanesthetic arousal times. Anesthesia was induced in all patients with thiopental and was maintained with $N_2O$-$O_2$. Atropine-neostigmine significantly delayed arousal for the first 30 minutes following cessation of anesthesia and reversal of neuromuscular blockade. The difference between the two mixtures following reversal of neuromuscular blockade is attributed to the fact that atropine is a tertiary amine that crosses the blood-brain barrier and delays arousal, whereas glycopyrrolate is a quaternary ammonium compound that does not cross this barrier.

**Key Words:** PARASYMPATHETIC NERVOUS SYSTEM: glycopyrrolate and atropine; NEUROMUSCULAR RELAXANTS: reversal; RECOVERY: glycopyrrolate and atropine.

---

A MIXTURE of atropine and neostigmine has been recommended for reversal of non-depolarizing neuromuscular blockade in man.[1-3] The mixture results in a transient initial tachycardia followed by bradycardia but without serious cardiac arrhythmias.[3] Glycopyrrolate-neostigmine has been suggested as an alternative mixture for reversal of neuromuscular blockade.[4, 5] It produces less initial tachycardia followed by less bradycardia than the atropine-neostigmine mixture. The incidence of arrhythmias is similar following either mixture.[4, 5] The antisialogogue action of glycopyrrolate-neostigmine mixture is superior to that of atropine-neostigmine.[5]

Glycopyrrolate is a quaternary ammonium compound that does not cross the blood-brain barrier,[6] whereas atropine is a tertiary amine which can cross the blood-brain barrier and hence may produce the central anticholinergic syndrome characterized by drowziness, disorientation, and hallucinations.[7] The present report scores and compares postoperative arousal times when glycopyrrolate-neostigmine and when atropine-neostigmine mixtures are used for reversal of neuromuscular blockade.

## Methods

Fifty-four healthy adult female patients undergoing gynecologic operations were studied. All patients

---

* Professor and Chairman, Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.

† Third Year Resident, Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.

‡ Assistant Professor, Department of Anesthesiology, American University of Beirut, Beirut, Lebanon.

§ Professor and Chairman, Department of Anesthesiology, University of Illinois, Chicago, Illinois.

Received from the Department of Anesthesiology, American University of Beirut, Beirut, Lebanon. Accepted for publication February 18, 1980.

Reprint requests to Dr. Baraka.

were teetotalers; none was receiving medications acting on the central nervous system. Patients were divided in a random fashion into two groups of 27 patients each. Both groups were comparable insofar as age, weight, and type and duration of anesthesia were concerned (Table 1).

All patients were premedicated with meperidine, 75 mg, and promethazine, 25 mg IM, 45 to 60 minutes prior to induction of anesthesia. In both groups, anesthesia was induced with thiopental, 4 mg/kg, followed by succinylcholine, 1.5 mg/kg. After tracheal intubation, anesthesia was maintained with 70% nitrous oxide in oxygen supplemented by the nondepolarizing neuromuscular blocking agent, alcuronium, 0.25 to 0.5 mg/kg.

In group 1, premedication was supplemented by atropine, 0.4 mg IV, immediately before induction; in group 2, glycopyrrolate, 0.2 mg, was given. At the end of the operation, the neuromuscular block was antagonized in group 1 by a mixture of atropine, 0.02 mg/kg, and neostigmine, 0.05 mg/kg; in group 2 a mixture of glycopyrrolate, 0.01 mg/kg, and neostigmine, 0.05 mg/kg, was used for antagonism.

Arousal following termination of anesthesia and antagonism of neuromuscular blockade was observed and scored at 5-minute intervals for the first half hour and at 10-minute intervals thereafter. Arousal was scored by a senior anesthesiologist unaware of the treatment administered. The scoring system used is shown in Table 2. Comparisons of arousal scores between the two groups were made using the test of significance of difference between two proportions.

## Results

The distribution of patients according to the arousal scores obtained in both the atropine-neostigmine and the glycopyrrolate-neostigmine groups at different time intervals following reversal of neuromuscular blockade, is illustrated in the histogram (Figure).

Five minutes following reversal of the neuromuscular relaxant, none of the patients were in stages 4 or 5; the majority of patients in both groups were in stage 3, i.e., asleep but responsive to verbal and painful stimulation (Table 3). In this stage were 59.2% of the patients given glycopyrrolate and 81.5% of the patients receiving atropine ($p > 0.05$).

As shown in Table 3, the rate of arousal from stage 3 was more rapid with glycopyrrolate than with atropine. At 10 minutes, 11.1% of the patients given glycopyrrolate were still in stage 3, in contrast with 59.2% of those given atropine ($p < 0.001$). At 15 minutes, only 3.7% of the patients given glycopyrrolate were still in stage 3, in contrast with 37% of those given atropine ($p < 0.01$).

After 15 minutes, as shown in Table 4, the percentage of patients who were completely awake, did not feel sleepy, and initiated conversation (stage 1) was significantly greater after glycopyrrolate than after atropine had been used. At 20 minutes, 44.4% of those given glycopyrrolate had reached stage 1, while only 18.3% of those given atropine had reached this stage ($p < 0.05$). At 25 minutes, 59.2% of the patients given glycopyrrolate had reached stage 1, while only 29.6% of those given atropine had reached this stage ($p < 0.05$). At 30 minutes, 66.6% of those given glycopyrrolate group had reached stage 1, while only 40% of those given atropine had reached this stage ($p = 0.05$). After 30 minutes, there was no significant difference between the two groups.

**TABLE 2**

**Arousal Scoring System**

| Stage | Description |
|---|---|
| 1 | Awake; does not feel sleepy and initiates conversation. |
| 2 | Awake, but feels sleepy and does not initiate conversation. |
| 3 | Asleep, but responds to both verbal and painful stimulation. |
| 4 | Asleep, but responds only to painful stimulation.* |
| 5 | Asleep, but does not respond to either verbal† or painful stimulation. |

* Painful stimulation = pinching the skin.

† Verbal stimulation = calling her name.

**TABLE 1**

**Mean Age, Weight, and Duration of Anesthesia of Groups 1 and 2***

|  | Mean age *yr* | Mean weight *kg* | Mean duration of anesthesia *min* |
|---|---|---|---|
| Group 1 (atropine) | 34.59 ± 12.21 | 63.19 ± 7.39 | 71.48 ± 47.41 |
| Group 2 (glycopyrrolate) | 37.11 ± 12.38 | 61.86 ± 9.25 | 68.92 ± 39.88 |
| *t* | 0.75 | 0.58 | 0.46 |
| *p* | NS | NS | NS |

* Values are means ± standard deviation. NS indicates no statistically significant difference.

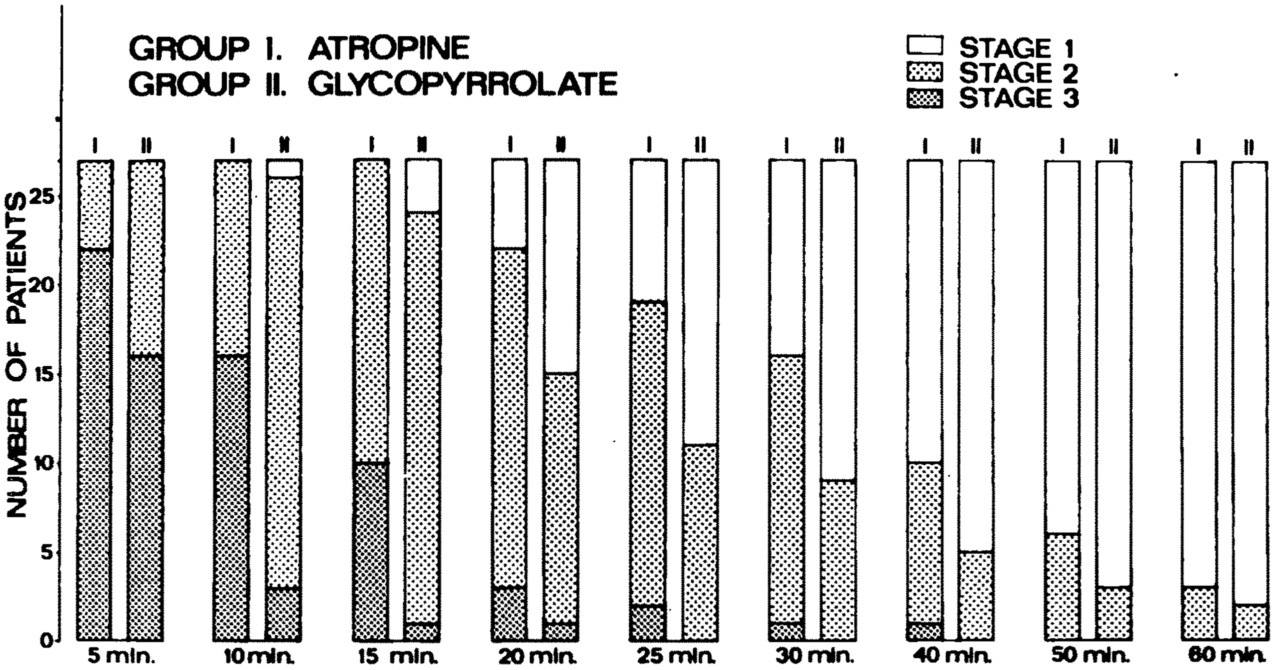


FIGURE. Histogram showing the distribution of patients according to the arousal scores obtained at different intervals following reversal of neuromuscular blockade. See Table 2 for definition of stages of arousal.

TABLE 3

**Patients in Both Groups* in Stage 3 (Asleep but Responsive to Both Verbal and Painful Stimulation) 5 to 15 minutes following Reversal**

| | Time following reversal | | | | | |
|---|---|---|---|---|---|---|
| | 5 Minutes | | 10 Minutes | | 15 Minutes | |
| | Atropine | Glycopyrrolate | Atropine | Glycopyrrolate | Atropine | Glycopyrrolate |
| No. of patients in stage 3 | 22 | 16 | 16 | 3 | 10 | 1 |
| Percentage | 81.5 | 59.2 | 59.2 | 11.1 | 37.0 | 3.7 |
| *p* | >0.05 | | <0.001 | | <0.01 | |

## Discussion

The present report demonstrates that arousal following thiopental induction of $N_2O$-$O_2$ anesthesia is more rapid when neuromuscular blockade is reversed with glycopyrrolate-neostigmine mixture than it is when atropine-neostigmine is used. This difference can be explained by the fact that glycopyrrolate is a quaternary ammonium compound that does not cross the blood-brain barrier, whereas atropine is a tertiary amine that can cross this barrier and block central cholinergic transmission.

Acetylcholine is a central neurotransmitter that affects arousal. It has an excitatory action on certain cortical cells,[8] and acts on cholino-reactive structures widely distributed in the pontomesencephalic reticular formation.[9] Arousal can be elicited by cholinomimetics and blocked by anticholinergics.[10] Thus, anticholinergics such as atropine that cross the blood-brain barrier can produce a central anticholinergic syndrome characterized by drowziness, disorientation, and hallucinations.[7] In unanesthetized patients, atropine in doses of 0.5 to 2.0 mg may cause a mental withdrawl of the patient from his surroundings, lethargy, a tendency to sleep, and diminution of the powers of concentration.[11] With larger doses, lethargy and dissociation are more frequent and may be associated with hallucinations.[7] These effects may be clinically important in patients recovering from general anesthesia, particularly in patients who are liable to develop disorientation such as children,[12] elderly patients,[13] or those receiving drugs that may be associated with the central anticholinergic syndrome (phenothiazines,[14] tricyclic antidepressants,[15] butyrophenones[16]).

We conclude that the glycopyrrolate-neostigmine mixture is preferable to atropine-neostigmine for reversal of neuromuscular blockade. Both neostigmine and glycopyrrolate are quaternary ammonium compounds that do not cross the blood-brain barrier, and hence the peripheral muscarinic side effects of neostigmine can be adequately[4, 5] and selectively coun-

**TABLE 4**

**Patients in Both Groups* Who Scored 1 (Completely Awake, Did Not Feel Sleepy and Initiated Conversation), 20 to 40 Minutes following Reversal**

| | Time following reversal | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 20 Minutes | | 25 Minutes | | 30 Minutes | | 40 Minutes | |
| | Atropine | Glycopyrrolate | Atropine | Glycopyrrolate | Atropine | Glycopyrrolate | Atropine | Glycopyrrolate |
| No. of patients in stage 1 | 5 | 12 | 8 | 16 | 11 | 18 | 17 | 22 |
| Percentage | 18.5 | 44.4 | 29.6 | 59.2 | 40.7 | 66.6 | 62.9 | 81.4 |
| *p* | <0.05 | | <0.05 | | =0.05 | | >0.1 | |

teracted by glycopyrrolate without affecting postanesthetic arousal.

## ACKNOWLEDGMENT

The authors express their appreciation to Dr. Huda C. Zurayk, Associate Professor of Biostatistics at the American University of Beirut, for performing the statistical analysis of the data.

## REFERENCES

1. Kemp SW, Morton HJV: The effect of atropine and neostigmine on the pulse rates of anaesthetized patients. Anaesthesia 17:170–175, 1962
2. Rosner V, Kepes ER, Foldes FF: The effects of atropine and neostigmine on heart rate and rhythm. Br J Anaesth 43:1066–1074, 1971
3. Baraka A: Safe reversal (2): Atropine-neostigmine mixtures: an electrocardiographic study. Br J Anaesth 40:30–36, 1968
4. Ramamurthy S, Shaker MH, Winnie AP: Glycopyrrolate as a substitute for atropine in neostigmine reversal of muscle relaxant drugs. Can Anaesth Soc J 19:399–411, 1972
5. Mirakhur RK, Dundee JW, Clarke RSJ: Glycopyrrolate-neostigmine mixture for antagonism of neuromuscular block: comparison with atropine-neostigmine mixture. Br J Anaesth 49: 825–829, 1977
6. Proakis, AG, Harris GB: Comparative penetration of glycopyrrolate and atropine across the blood-brain and placental barriers in anesthetized dogs. Anesthesiology 48:339–344, 1978
7. Longo VG: Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacol Rev 18:965–996, 1966
8. Krnjevic MB: Chemical transmission and cortical arousal. Anesthesiology 28:101–105, 1967
9. Baraka A, Harik S: Reversal of central anticholinergic syndrome by galanthamine. JAMA 238:2293–2294, 1977
10. Funderburk WH, Case TJ: The effect of atropine on cortical potentials. Electroencephalogr Clin Neurophysiol 3:213–223, 1951
11. Shutt LE, Bowes JB: Atropine and hyoscine. Anaesthesia 34: 476–490, 1979
12. Dauchot P, Gravenstein JS: Effects of atropine on the electrocardiogram in different age groups. Clin Pharmacol Ther 12: 274–280, 1971
13. Smith DS, Orkin FK, Gardner SM, et al: Prolonged sedation in the elderly after intraoperative atropine administration. Anesthesiology 51:348–349, 1979
14. Bernards W: Reversal of phenothiazine induced coma with physostigmine. Anesth Analg 52:938–941, 1973
15. Burks JS, Walter JE, Rumack BH, et al: Tricyclic antidepressant poisoning: reversal of coma, choreoathetosis and myoclonus by physostigmine. JAMA 230:1405–1407, 1974
16. Bidwai AV, Cornelius LR, Stanley TH: Reversal of Innovar-induced postanesthetic somnolence and disorientation with physostigmine. Anesthesiology 44:249–252, 1976

ANESTH ANALG
59:435–437, 1980

# Lidocaine or Thiopental for Rapid Control of Intracranial Hypertension?

**Robert F. Bedford, MD,* John A. Persing, MD † Louis Pobereskin, MD,† and Albert Butler, MD‡**

---

BEDFORD, R. F., PERSING, J. A., POBERESKIN, L., AND BUTLER, A.: Lidocaine or thiopental for rapid control of intracranial hypertension? Anesth Analg 59:435–437, 1980.

The effectiveness of intravenously administered lidocaine for rapid control of acute intracranial hypertension was compared to the effectiveness of thiopental in 20 patients with brain tumors undergoing craniotomy. Despite normal radial arterial and intracranial pressures (ICP) after induction of $N_2O$-$O_2$-morphine anesthesia, mean ICP increased from 1C.8 torr ± 1.5 SE to 31 torr ± 2.3 SE ($p < 0.001$) in response to application of a pin-holder or scalp incision. To treat the elevated ICP a bolus injection of lidocaine, 1.5 mg/kg IV, was given to 10 patients, whereas the other 10 received thiopental, 3 mg/kg IV. Lidocaine reduced ICP 15.7 torr ± 5.6 SE ($p < 0.025$) but did not significantly affect mean arterial pressure. In contrast, thiopental lowered ICP 18.4 torr ± 9.6 SE ($p < 0.02$) and also lowered mean arterial pressure by 26.1 torr ± 9.6 SE ($p < 0.025$). Mean time for injection of medication to ICP nadir was 66 seconds ± 10 SE after lidocaine versus 48 seconds ± 9 SE after thiopental ($p > 0.20$). It is concluded that lidocaine is as effective as thiopental for rapid reduction of intraoperative intracranial hypertension but that it causes less cardiovascular depression. Lidocaine may be of particular benefit to patients with both intracranial hypertension and marginal circulatory function.

**Key Words:** ANESTHESIA: neurosurgical; BRAIN: intracranial pressure; ANESTHETICS, Local: lidocaine; ANESTHETICS, Intravenous: thiopental.

---

PREVENTION and treatment of acute intracranial hypertension is one of the primary goals in the neuroanesthetic care of patients with space-occupying intracranial lesions. Although use of barbiturates for control of intracranial pressure (ICP) has become accepted practice,[1] their associated depression of the cardiovascular, respiratory, and central nervous systems renders them less than ideal agents for this purpose. Recently we observed a profound reduction in ICP following bolus intravenous administration of lidocaine for treatment of intraoperative ventricular irritability. This report describes the intravenous use of lidocaine for treatment of increased ICP comparing these observations with data obtained during thiopental treatment of acute intracranial hypertension.

## Methods and Materials

The protocol for the use of lidocaine was reviewed by the local human studies committee, and informed consent was obtained from both the patients and their nearest relative. All 20 patients had intracranial mass lesions estimated to be larger than 2 cm in diameter by CAT-scan. All were receiving steroid therapy and were scheduled for elective craniotomy. Preoperative medication consisted of intramuscular morphine, 0.1 mg/kg, diazepam, 0.1 mg/kg, and atropine, 0.4 mg.

A subarachnoid pressure screw and radial arterial

---

* Assistant Professor of Anesthesiology and Neurological Surgery.

† Research Fellow, Department of Neurological Surgery.

‡ Associate Professor of Neurological Surgery.

Received from the Departments of Anesthesiology and Neurological Surgery, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication February 28, 1980. Presented at the 54th Congress of the International Anesthesia Research Society, March 9–13, 1980, Reno, Nevada.

Reprint requests to Dr. Bedford, Department of Anesthesiology.

and central venous cannulae were placed under local anesthesia in the operating room and pressures were continuously monitored (Bentley model 800 transducers) and recorded (Brush model 440 polygraph). Intracranial compliance was estimated from the pressure change induced by an injection of saline solution, 1 or 2 ml given in 5 seconds through the subarachnoid pressure screw. General anesthesia then was induced with thiopental (3 to 4 mg/kg) and nitrous oxide (70% in oxygen) and was supplemented with intravenous morphine 0.1 to 0.5 mg/kg. Endotracheal intubation was facilitated with pancuronium (0.1 mg/kg) and ventilation was controlled to maintain a constant end-tidal $CO_2$ concentration (33.2 torr ± 1.9 SE).

Despite what appeared to be satisfactory general anesthesia and normal resting arterial and intracranial pressure levels, significant intracranial hypertension (>25 torr) occurred in response to either scalp incision or application of the pin head-holder. After 30 seconds of sustained intracranial hypertension, 10 patients were treated with an intravenous bolus of lidocaine, 1.5 mg/kg, whereas the other 10 patients were given thiopental, 3 mg/kg. Changes in intracranial and mean arterial pressure as well as the time-span from drug injection to ICP nadir were tabulated.

Statistical comparisons were performed using Student's *t*-tests for paired and nonpaired data.

## Results

The groups treated with thiopental and lidocaine proved to be similar with regard to tumor type, age, intracranial compliance, and end-tidal $CO_2$ concentration ($P_{ET}CO_2$) (Table 1). The time for drug injection to ICP nadir was slightly longer after intravenous lidocaine than after thiopental; a difference which was apparent clinically although not statistically significant.

Both lidocaine and thiopental caused a significant reduction in ICP to values which were indistinguishable from those observed prior to surgical stimulation (Fig 1). Thiopental simultaneously caused a 26 torr reduction in mean arterial blood pressure, whereas blood pressure remained unchanged following intravenous lidocaine (Fig 2). In most instances ICP did not again increase >20 torr before the cranium was opened, so that it was not possible to document a time-action relationship for either lidocaine or thiopental. Fig 3, however, illustrates the record of a patient who redeveloped intracranial hypertension after successful treatment with thiopental. Lidocaine produced a more gradual reduction in ICP which then persisted until the cranium was opened.

**TABLE**

**Treatment of Acute Intracranial Hypertension Thiopental versus Lidocaine**

| | Thiopental | Lidocaine |
|---|---|---|
| Patient age (yr) | 47.5 ± 5.0 | 51.1 ± 4.4 |
| IC compliance (torr/ml) | 6.0 ± 0.9 | 4.0 ± 1.0 |
| $P_{ET}CO_2$ (torr) | 32.6 ± 1.9 | 33.7 ± 1.5 |
| Time from injection to ICP nadir (sec) | 48 ± 9 | 66 ± 10 |

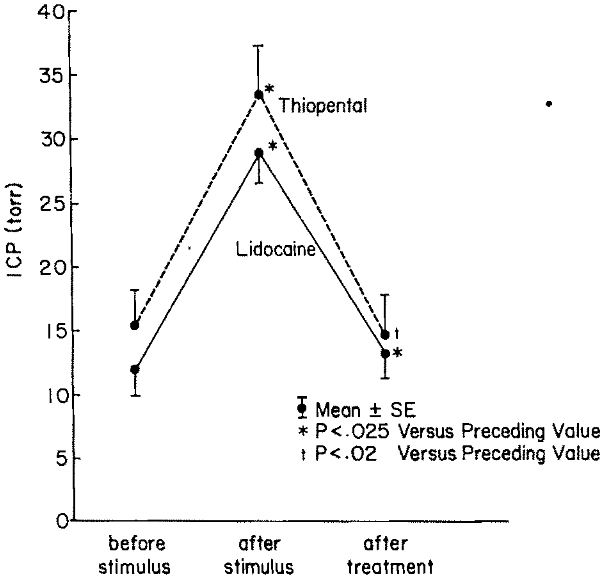


FIG 1. ICP response to surgical stimulation and subsequent treatment with lidocaine and thiopental.

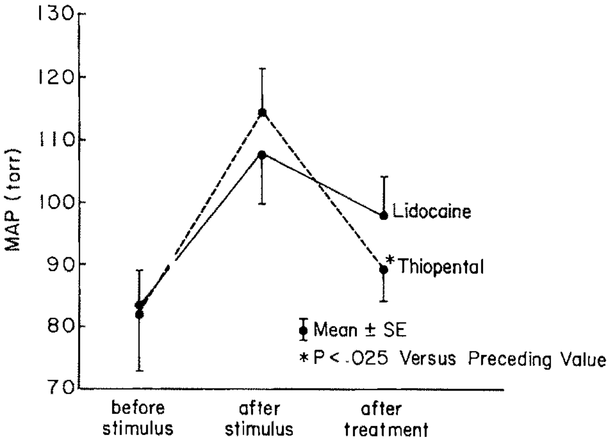


FIG 2. Mean arterial pressure (MAP) response to surgical stimulation and subsequent treatment with lidocaine and thiopental.

## Discussion

Previous studies have shown that intravenous lidocaine prevents intracranial hypertension when given to anesthetized patients with brain tumors before endotracheal intubation[2] or to comatose patients with closed head injuries before endotracheal suction-

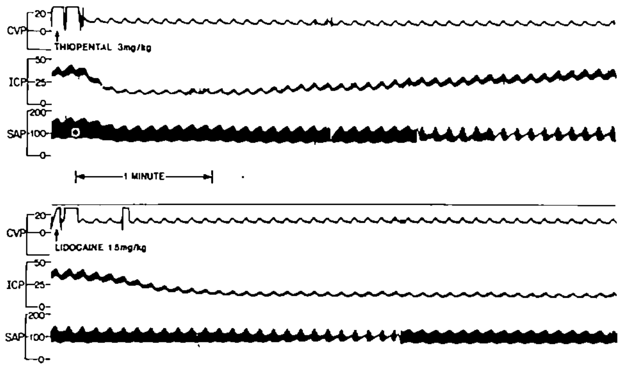


FIG 3. Record of ICP, systemic arterial pressure (SAP), and central venous pressure (CVP) in a patient with persistent intracranial hypertension treated first with thiopental and then with lidocaine.

ing.[3] Lidocaine has been shown to be an effective cough suppressant,[4] and in the presence of tracheal stimulation we believe its effect on ICP occurs partially on this basis. The effect observed in this report, however, appears to be mediated through an anesthetic action similar to that described for barbiturates.[1] Intravenous lidocaine potentiates inhalation anesthetics,[5] reduces both cerebral oxygen consumption and cerebral blood flow, and increases cerebrovascular resistance.[6] Presumably ICP thus decreases in response to a reduction in cerebral blood volume.

Prior to undertaking this study we had observed eight patients with brain tumors who developed elevated ICP (31.1 torr ± 1.9 SE) while undergoing craniotomy during $N_2O$-$O_2$-morphine anesthesia. The mean duration of the increase in ICP in the absence of pharmacologic intervention was 236 seconds ± 43 SE. Thus, it appears that both lidocaine and thiopental are capable of gently reducing the duration of surgically induced intracranial hypertension and, therefore, shorten the time when the brain is prone to herniation or low cerebral perfusion pressure (mean arterial pressure-intracranial pressure).

Cardiovascular function is depressed by both thiopental[7] and lidocaine.[8] Our data indicate that at doses that are equally effective for control of intracranial hypertension during nitrous oxide-morphine anesthesia, arterial pressure is changed minimally by lidocaine, whereas it is significantly reduced by thiopental. This could be of particular importance during the care of patients with increased ICP and arterial hypotension in whom a further reduction in arterial pressure may compromise cerebral perfusion. Similarly, when halothane or enflurane is administered to control arterial hypertension and tachycardia, lidocaine successfully decreases ICP without further decreasing arterial pressure (R. F. Bedford, unpublished data).

What about anesthetic management for the patient undergoing craniotomy without intracranial pressure monitoring? Although prophylactic administration of thiopental will prevent intracranial hypertension, its cardiovascular effects may make this a risky undertaking in an elderly or critically ill patient. In contrast, lidocaine can be given prophylactically before noxious stimulation; it effectively and safely prevents increased ICP in patients with either brain tumors[2] or closed head injuries.[3] As a result, we now routinely administer lidocaine, 1.5 mg/kg IV, 1 minute before endotracheal intubation or surgical stimulation whenever patients are thought to be at risk for developing reactive intracranial hypertension.

In conclusion, we recommend the use of intravenous lidocaine for rapid control of intracranial hypertension in anesthetized patients with brain tumors. The effect of lidocaine on ICP is similar to that observed with thiopental, but lidocaine causes less depression of cardiovascular function.

## REFERENCES

1. Shapiro HR, Galindo A, Whyte SR, et al: Rapid intraoperative reduction of intracranial pressure with thiopentone. Br J Anaesth 45:1057–1062, 1973
2. Bedford RF, Winn HR, Tyson G, et al: Lidocaine prevents increased intracranial pressure after endotracheal intubation, in Intracranial Pressure IV. Edited by K Shulman, A Marmarou, JD Miller, et al. New York, Springer Verlag, in press 1980
3. Donegan MF, Bedford RF, Dacey R: Lidocaine for prevention of intracranial hypertension. Anesthesiology 51:S201, 1979
4. Steinhaus JE, Gaskin L: A study of lidocaine as a suppressant of cough reflex. Anesthesiology 24:285–290, 1963
5. Himes RS, DiFazio CA, Burney RG: Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology 47:437–440, 1977
6. Sakabe T, Maekawa T, Ishikawa T, et al: The effects of lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. Anesthesiology 40:433–441, 1974
7. Etsten BE, Li TH: Hemodynamic changes during thiopental anesthetic in humans: cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume. J Clin Invest 34:500–510, 1955
8. Schumacher RR, Lieberson AD, Childress RH, et al: Hemodynamic effects of lidocaine in patients with heart disease. Circulation 37:965–972, 1968

ANESTH ANALG
59:438–441, 1980

# Hemodynamic Effects of Diazepam and Diazepam-Nitrous Oxide in Patients with Coronary Artery Disease

**Richard L. McCammon, MD,* John C. Hilgenberg, MD,* and Robert K. Stoelting, MD†**

---

MCCAMMON, R. L., HILGENBERG, J. C., AND STOELTING, R. K.: Hemodynamic effects of diazepam and diazepam-nitrous oxide in patients with coronary artery disease. Anesth Analg 59: 438–441, 1980.

Circulatory responses following intravenous diazepam (0.5 mg/kg) and the subsequent addition of 50% nitrous oxide were studied in 14 patients undergoing elective aortocoronary saphenous vein bypass operations. No patient was receiving propranolol. Preanesthetic medication was with morphine and scopolamine. Diazepam was continuously infused over a 10-minute period. At the conclusion of the infusion, systolic and mean arterial pressures were 13% lower than control awake values ($p < 0.05$). Heart rate, cardiac output, right atrial pressure, pulmonary arterial pressure, pulmonary artery occluded pressure, and systemic and pulmonary vascular resistance were not changed. The subsequent addition of nitrous oxide resulted in no further statistically significant changes except for a 2.4 torr increase in right atrial pressure ($p < 0.05$). In contrast, previous data collected from similar patients demonstrated significant reductions in blood pressure and cardiac output while systemic and pulmonary vascular resistance and pulmonary artery occluded pressure were increased when nitrous oxide was added following the administration of morphine (1 to 2 mg/kg). It is concluded that the observed minimal circulatory changes following diazepam administration and the subsequent addition of nitrous oxide make diazepam-nitrous oxide a valuable alternative to a morphine-nitrous oxide induction of anesthesia in patients with coronary artery disease.

**Key Words:** HYPNOTICS, Benzodiazepines: diazepam; ANESTHETICS, Gases: nitrous oxide; ANESTHESIA: cardiovascular.

---

INTRAVENOUS morphine has achieved popularity in the anesthetic management of patients with cardiac disease. In critically ill patients intravenous morphine (0.5 to 2 mg/kg) is appropriate as a sole anesthetic, but not for more healthy patients. Although an excellent analgesic, morphine in these dose ranges does not consistently produce loss of consciousness and total amnesia is not certain.[1] The addition of nitrous oxide has been advocated to overcome this problem. However, nitrous oxide administration in the presence of morphine (0.6 to 2.8 mg/kg) results in dose-related cardiovascular depression.[2] Also, hypotension may occur during or immediately following infusion of morphine (1 mg/kg at 10 mg/min).[3] Likewise, chest wall rigidity may occur secondary to narcotic administration resulting in a marked decrease in chest wall compliance or apnea.

The present study evaluated circulatory responses following intravenous diazepam (0.5 mg/kg) and the subsequent addition of 50% nitrous oxide in patients

---

* Assistant Professor.

† Professor and Chairman.

Received from the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana 46223. Accepted for publication March 5, 1980.

Reprint requests to Dr. McCammon.

with coronary artery disease to determine whether diazepam might have advantages over morphine in the anesthetic management of patients with heart disease.

## Methods

Fourteen patients undergoing elective aortocoronary saphenous vein bypass graft surgery were studied. The study was approved by the Indiana University School of Medicine Human Subjects Committee. Digitalis and diuretics had been discontinued 48 hours prior to surgery and no patient was receiving propranolol. Preanesthetic medication consisted of morphine (10 to 15 mg) and scopolamine (0.4 to 0.6 mg) intramuscularly 90 minutes prior to anesthetic induction.

Upon arrival in the operating room, electrocardiogram leads were attached and peripheral intravenous lines and a radial artery catheter were placed. A 7 Fr Swan-Ganz thermodilution, flow-directed catheter was introduced into the pulmonary circulation via the right internal jugular vein. The patients then breathed 50% oxygen in nitrogen by mask as determined by an oxygen analyzer from the anesthetic circuit. The following measurements were then made: systolic, diastolic, and mean arterial pressures (SBP, DBP, MAP), cardiac output (CO), mean pulmonary arterial pressure (PAP), mean right atrial pressure (RAP), pulmonary artery occluded pressure (PAo), and temperature (thermistor of Swan-Ganz catheter). Systemic and pulmonary vascular resistance (SVR, PVR), cardiac index (CI), stroke index (SI), and heart rate-systolic blood pressure product (RPP) were calculated.

After these control measurements, diazepam (0.5 mg/kg) was administered intravenously over 10 minutes while the patients continued to breathe 50% oxygen. Measurements were repeated at the conclusion of diazepam. Subsequently, nitrous oxide (50%) was administered by mask while the patients breathed spontaneously. Measurements, including arterial blood gases, were repeated after 10 minutes of nitrous oxide administration. Although end tidal nitrous oxide concentrations were not measured, it has been demonstrated that end tidal concentrations approach 90% of inspired concentrations within 3 to 5 minutes of administration of nitrous oxide.[3] Data were analyzed using analysis of variance; $p < 0.05$ was considered statistically significant.

At the completion of the study, endotracheal intubation was facilitated with succinylcholine and all patients were subsequently given either morphine (0.25 to 1.0 mg/kg) or a potent inhalation agent as dictated by circulatory responses occurring during the operative procedure.

## Results

The cardiovascular effects of intravenous diazepam and the subsequent addition of nitrous oxide are summarized in the Table. SBP and MAP decreased 13% ($p < 0.05$) following diazepam infusion while HR, CO, CI, RAP, PAP, PAo, SVR, PVR, and RPP did not change significantly from awake control values.

When compared to measurements at the conclusion of diazepam administration, the addition of nitrous oxide resulted in no further changes except for an increase of 2.4 torr in RAP ($p < 0.05$). $Pa_{O_2}$ and $Pa_{CO_2}$ at the conclusion of diazepam-nitrous oxide administration ranged from 114 to 297 torr (mean 187) and 41 to 51 torr (mean 45), respectively. No patient became apneic nor was there any change in chest wall compliance noted.

Comparing values after diazepam-nitrous oxide administration with awake control measurements revealed small but significant ($p < 0.05$) reductions in SBP, MAP, RPP, CO, and CI. Clinically, all patients failed to respond to verbal commands at the conclusion of the diazepam-nitrous oxide administration period. Likewise, no patient had any recall of intraoperative events.

## Discussion

These data demonstrate that intravenous diazepam (0.5 mg/kg) results in minimal circulatory changes when administered over 10 minutes to patients with coronary artery disease. The only statistically significant change from awake values was the 13% decrease in SBP and MAP.

The reported hemodynamic effects following diazepam infusion depend on dosage, rapidity of administration, concomitantly administered drugs, and basal physiologic state of the patient. The minimal reductions in MAP and CI noted in our study agree with the findings in a previous report describing patients with cardiac disease receiving diazepam (0.6 mg/kg) intravenously for induction of anesthesia prior to myocardial revascularization.‡ In patients

---

‡ Prakish R, Thruer R, Vargar A, et al: Cardiovascular effect of diazepam in patients for aorto-coronary saphenous vein bypass surgery. Scientific Abstracts of the American Society of Anesthesiologists, 1976, San Francisco, pp 263–264.

**TABLE**

**Hemodynamic Effects of Diazepam and Diazepam-Nitrous Oxide in Patients with Coronary Artery Disease**

| | Awake | Diazepam (0.5 mg/kg) | Nitrous oxide (50%) |
|---|---|---|---|
| Heart rate (beats/min) | 66 ± 3 | 68 ± 2 | 65 ± 2 |
| Systolic arterial pressure (torr) | 144 ± 4 | 125 ± 4* | 121 ± 4* |
| Diastolic arterial pressure (torr) | 81 ± 2 | 74 ± 3 | 75 ± 3 |
| Mean arterial pressure (torr) | 102 ± 3 | 91 ± 3* | 91 ± 3* |
| Right atrial pressure (torr) | 8.1 ± 1.2 | 7.2 ± 0.2 | 9.6 ± 1.4† |
| Systolic pulmonary arterial pressure (torr) | 25.1 ± 1.8 | 23.7 ± 1.3 | 23.7 ± 1.4 |
| Diastolic pulmonary arterial pressure (torr) | 13.8 ± 1.3 | 12.7 ± 0.9 | 13.6 ± 0.8 |
| Mean pulmonary arterial pressure (torr) | 18.4 ± 1.4 | 16.3 ± 0.9 | 17.2 ± 0.2 |
| Pulmonary artery occluded pressure (torr) | 11.5 ± 1.1 | 10.6 ± 1.2 | 11.9 ± 1.2 |
| Cardiac output (L/min) | 5.3 ± 0.3 | 5.1 ± 0.3 | 4.8 ± 0.3* |
| Cardiac index (L/min/$m^2$) | 2.8 ± 0.1 | 2.7 ± 0.1 | 2.5 ± 0.1* |
| Stroke index (ml/beat/$m^2$) | 43.1 ± 1.8 | 40.6 ± 1.7 | 39.9 ± 2.6 |
| Systemic vascular resistance (dynes·sec·$cm^{-5}$) | 1391 ± 97 | 1344 ± 120 | 1377 ± 128 |
| Pulmonary vascular resistance (dynes·sec·$cm^{-5}$) | 101 ± 11 | 95 ± 9 | 97 ± 15 |
| Heart rate-systolic blood pressure product | 9578 ± 558 | 8471 ± 418 | 7743 ± 292* |
| $Pa_{O_2}$ | | | 187 ± 46 |
| $Pa_{CO_2}$ | | | 44.6 ± 1.3 |
| pH | | | 7.36 |

* $p < 0.05$ compared with awake.
† $p < 0.05$ compared with diazepam.

without known cardiovascular disease, induction of anesthesia with intravenous diazepam (0.45 mg/kg) had no significant effect on MAP[4] while larger diazepam induction doses (0.8 mg/kg) decreased MAP and CO.[5] Systemic vascular resistance did not change following this larger diazepam dose.

From previous work it may be concluded that 0.5 mg/kg of diazepam intravenously and 1.1 mg/kg of morphine intravenously represent approximately equieffective dosages in terms of their ability to decrease MAC in man.[6]§ In comparable patients with coronary artery disease, an induction regimen consisting of morphine alone (1 mg/kg) decreased MAP 8% and had no significant effect on CI and SVR,[3] findings similar to those obtained in the present study following diazepam.

It has been reported[3] that precipitous hypotension requiring vasopressors occurred during or following morphine infusion (1 mg/kg at 10 mg/min) in six of 20 patients with cardiac disease. Although Falk et al[7] have reported a case of precipitous hypotension following the intravenous administration of 10 mg of diazepam over 30 seconds accompanied by the simultaneous administration of 50% nitrous oxide in a patient with coronary artery disease, hypotension has been reported less frequently following diazepam than after morphine. No patient required vasopressors during or after diazepam administration in the present study.

The addition of 50% nitrous oxide following diazepam in this study did not statistically change any circulatory variable as compared with measurements after diazepam except for a 2.4 torr increase in RAP. Comparison of measurements of cardiovascular function after diazepam-nitrous oxide with awake control measurements revealed small but statistically significant reductions in SBP (13%), MAP (11%), and CI (11%) while SVR did not change. The effects in cardiovascular function that might occur as a function of time following 0.5 mg/kg of diazepam intravenously if nitrous oxide had not been administered were not studied. Conceivably, if cardiovascular depression had occurred as a function of time following completion of the infusion of diazepam but in the absence of nitrous oxide, then the absence of further changes in cardiovascular function observed by us when nitrous oxide was administered, would indicate that nitrous oxide actually had a stimulatory effect. Although we cannot disprove this possibility, it seems unlikely in view of reports[8, 9] that described cardiovascular effects 15 to 25 minutes following intravenous diazepam administration (0.1 mg/kg) in patients with coronary artery disease. These studies documented either no further change or a return to control values in those cardiovascular parameters studied 15 to 25 minutes after diazepam administration compared to those measurements taken 5 minutes after diazepam administration.

---

§ Fraioli R, Sheffer L, Steffenson J: The MAC equivalent of morphine. Scientific Abstracts of the American Society of Anesthesiologists, 1973, San Francisco, pp 253–254.

We believe comparisons of cardiovascular changes observed when nitrous oxide was added to diazepam in this study and changes in studies with similar experimental protocols which have studied nitrous oxide following morphine are clinically pertinent. Specifically, Lappas et al[10] found the addition of 50% nitrous oxide following 2 mg/kg of morphine intravenously resulted in a similar decrease in MAP (9.5%) but a greater magnitude of depression of CI (23%) than we noted with diazepam-nitrous oxide. Similarly, Stoelting and Gibbs[3] noted a greater decrease in CI (34%) when 60% nitrous oxide was administered following 1 mg/kg of morphine intravenously when compared to our results with diazepam-nitrous oxide. Further, McDermott and Stanley[2] demonstrated that patients with cardiac disease who received an average dose of 1.7 mg/kg of morphine (0.6 to 2.8 mg/kg-range) exhibited dose-related depressions in cardiac output and stroke volume with incremental increases in concentrations of nitrous oxide administered (10% to 50%). Studies suggest that the cardiovascular changes produced by nitrous oxide are exaggerated in the presence of morphine, an effect not observed in this study when nitrous oxide was added to diazepam.

The increase in mean $Pa_{CO_2}$ after diazepam-nitrous oxide administration to 44.6 torr is similar to that previously observed following morphine infusion (1 mg/kg) in patients with coronary artery disease.[3] Nevertheless, rapid infusion of morphine may be associated with a decrease in chest wall compliance or apnea and large increases in $Pa_{CO_2}$. In contrast, no patient in our study became apneic nor was there any clinically detectable change in chest wall compliance, and the maximum observed increase in $Pa_{CO_2}$ was only 51 torr.

In this study, diazepam alone and diazepam plus 50% nitrous oxide had no significant effect on the pulmonary circulation. On the other hand, when nitrous oxide is added to morphine (2 mg/kg) PAP, PAo, and PVR increased.[10] These changes were attributed to alpha-adrenergic stimulation produced by nitrous oxide. Our data suggest that this response does not occur when nitrous oxide is preceded by diazepam.

We do not intend to imply that the results of this study indicate that diazepam-nitrous oxide is appropriate as the sole anesthetic for patients with cardiac disease. In fact, following induction of anesthesia and intubation all patients were given either supplemental morphine or a potent inhalation agent during the operative procedure. We do conclude, however, that induction of anesthesia with diazepam-nitrous oxide in patients undergoing myocardial revascularization is a practical alternative to morphine-nitrous oxide and may offer several advantages. These include minimal cardiovascular changes during induction, a lesser incidence of chest wall rigidity or apnea, good reliability in producing loss of consciousness and amnesia, and absence of deleterious effects on the pulmonary circulation.

## REFERENCES

1. Lowenstein E: Morphine "anesthesia"—a perspective. Anesthesiology 35:563-565, 1971
2. McDermott RW, Stanley TH: The cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 41:89-91, 1974
3. Stoelting RK, Gibbs PS: Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary artery disease. Anesthesiology 38:45-52, 1973
4. Dechene JP, Destrosiers R: Diazepam in pulmonary surgery. Can Anaesth Soc J 16:162-166, 1969
5. Rao S, Sherbaniuk RW, Prasad K, et al: Cardiopulmonary effects of diazepam. Clin Pharmacol Ther 14:182-189, 1972
6. Perisho JA, Buechel DR, Miller RD: The effect of diazepam (Valium) on minimum alveolar anaesthetic requirement (MAC) in man. Can Anaesth Soc J 18:536-539, 1971
7. Falk RB Jr, Denlinger JK, Nahrwold NL, et al: Acute vasodilation following induction of anesthesia with intravenous diazepam and nitrous oxide. Anesthesiology 49:149-150, 1978
8. Coté P, Campeau L, Bourassa M: Therapeutic implications of diazepam in patients with elevated left ventricular filling pressure. Am. Heart J 91:747-751, 1976
9. Markiewicz W, Hunt S, Harrison D, et al: Circulatory effects of diazepam in heart disease. Clin Pharmacol 16:637-643, 1976
10. Lappas DG, Mortimer JB, Laver MB, et al: Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary artery surgery. Anesthesiology 43:61-69, 1975

# Acute Respiratory Distress as a Complication of Left Ventricular Cardiac Catheterization

D. A. Cozanitis, BScPharm, MB, ChB, MD, DTM&H, and J. Heinonen, MD

Complications of cardiac catheterization are numerous and well documented.[1] However, as no report of cardiac catheterization directly resulting in respiratory distress has been found, we present such a life-threatening complication here.

## Case Report

The patient, a 27-year-old, 68 kg, 179-cm tall bank worker and mother of one child, had been admitted for investigation after having previously suffered two bouts of syncope. The patient had a history of hypercholesterolemia first diagnosed when she was 23 years old. T waves were inverted in leads II, III, and $aV_F$ of the electrocardiogram. As cardiomyopathy was suspected, it was decided that left ventricular cardiac catheterization was indicated. Passage of the catheter through the right brachial artery met with some degree of resistance before the tip of the catheter was placed into the left ventricle. Intracardiac injection of the contrast media was immediately followed by the onset of dyspnea and stridor. As it was thought that a reaction to the contrast media had occurred, hydrocortisone (250 mg) was injected via the catheter. There was no improvement and the catheterization procedure was abandoned. An anaesthetist was called for consultation.

On examination, the patient was complaining of dyspnea, and because the chain she wore around her neck was becoming uncomfortably tight, it was removed. She denied a history of thyroid disease. Blood pressure in the left arm was 130/80 mm Hg. Pronounced stridor was evident, but auscultation of the chest revealed nothing abnormal. Her hemoglobin level at that time was 12.3 gm/100 ml. She was given 35% oxygen via a face mask, an intravenous infusion of electrolyte solution was begun, and periodic measurement of the neck, then 40 cm, was initiated. She was moved to the recovery room. On reaching the recovery room, her breathing had deteriorated and she was ventilated by a mask using a non-rebreathing system. Oral endotracheal intubation with a rubber Magill tube failed as an apparent obstruction in the trachea would not permit passage. The patient became deeply cyanotic and began to convulse; bradycardia developed. She was again ventilated with the mask and atropine (1 mg) was given intravenously. A bronchoscope was then successfully introduced through which oxygenation could be carried out. Examination through the bronchoscope showed a retrotracheal expansion almost occluding the lumen of the trachea some 8 cm above the carina. A chest x-ray revealed widening of the mediastinum (Fig. 1). After the patient regained consciousness, diazepam (5 mg) was given intravenously and the bronchoscope was quickly replaced by a latex armored nasotracheal tube. Auscultation of the chest showed good air entry bilaterally and the patient indicated that her ventilation was sufficient. Surgical consultation advised immediate surgery, but it was decided to move the patient to the intensive care unit for observation. In the ICU she did well. On the following morning after a chest x-ray showed that the mediastinum had narrowed, the endotracheal tube was withdrawn 7 cm, and after 90 minutes of observation the trachea was extubated. Another chest x-ray was taken at that time (Fig 2). Her hemoglobin had decreased 1.3 gm/100 ml, suggesting that she had hemorrhaged. The circumference of the patient's neck had diminished by 1 cm. Vital signs, serum electrolyte levels, and arterial blood gas tensions being well within normal values, she was returned to her ward in satisfactory condition.

## Discussion

It is probable that either the subclavian or the brachiocephalic artery was perforated during inser-

---

Received from the Department of Anaesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki 29, Finland. Accepted for publication January 23, 1980.

Reprint requests to Dr. Cozanitis.

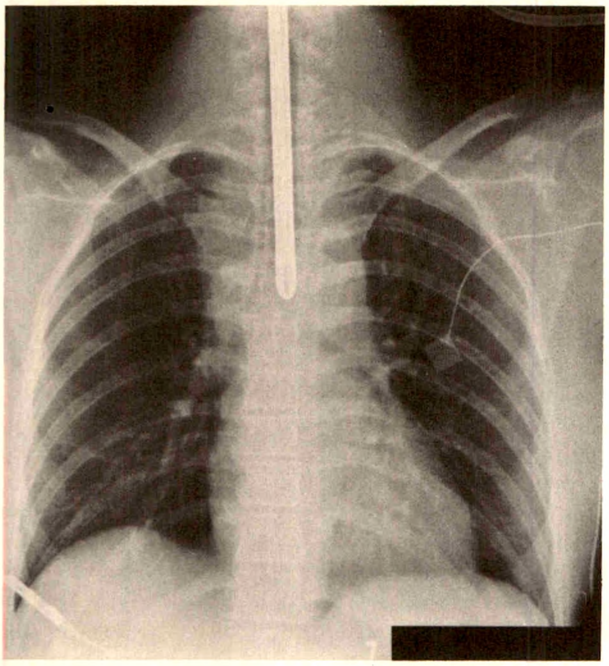


FIG 1. Chest x-ray showing wide mediastinum and bronchoscope in situ.

tion of the catheter. An arteriogram would have been helpful in confirming the diagnosis. The resulting hematoma, which encroached on and compressed the trachea, prevented passage of the soft, rubber Magill tube. The availability of the bronchoscope was lifesaving. We strongly emphasize that when an obstruction of this nature, whether by instrumentation or by invasion (for example by a tumor into a blood vessel), is suspected, that a noncollapsible tracheal tube be placed as early as possible. The decision to observe the patient rather than to subject her to surgery proved, in this case at least, to be correct.

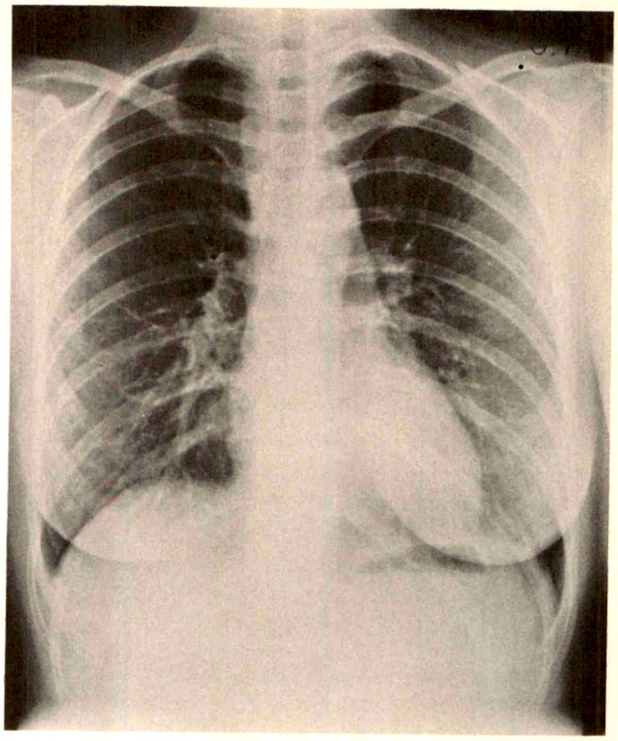


FIG 2. Chest x-ray taken the following day. Mediastinum is reduced in area.

In summary, perforation of an artery remote from the site at which arterial puncture had been performed for left ventricular catheterization resulted in hematoma formation which produced stridor and tracheal obstruction but which was successfully handled by conservative management.

## REFERENCE

1. Grossman W: Cardiac catheterization by direct exposure of artery and vein, in Cardiac Catheterization and Angiography. Philadelphia, Lea and Febiger, 1974, pp 22–23

ANESTH ANALG
59:444-446, 1980

# Succinylcholine-Induced Hyperkalemia in a Patient with Parkinson's Disease

**Glenn P. Gravlee, MD***

Succinylcholine has been reported to cause hyperkalemia when given to patients with various neuromuscular diseases.[1,2] The following case report describes hyperkalemia during succinylcholine administration in a patient with Parkinson's disease. No previous report of this possible association was found in a search of the literature.

## Case Report

A critically ill 64-year-old 72 kg white man was transferred from an outlying hospital for further evaluation and consideration for coronary artery bypass surgery. He had been reasonably well until 6 days previously when he suffered an extensive anterior myocardial infarction complicated by persistent chest pain and pulmonary edema responding poorly to aggressive therapy with digoxin, furosemide, and nitrates. Past history included Parkinson's disease diagnosed in 1973 and well controlled with carbidopa/levodopa (Sinemet), 25/250 mg orally twice a day. Lumbar laminectomies had been performed in 1967 and 1972 under general anesthesia without known untoward incident. No residual neurologic deficit was reported after either operation.

Shortly after arrival at this institution an intra-aortic balloon pump was inserted for counterpulsation because of continued episodic chest pain, increasing ST segment elevation in the anterior leads, and rising pulmonary capillary wedge (PCW) pressures responding only to high-dose intravenous nitroglycerin. These changes were attenuated or eliminated by counterpulsation so that the nitroglycerin infusion could be discontinued. Medications then included digoxin, quinidine gluconate, isosorbide dinitrate, furosemide, diazepam, carbidopa/levodopa, trihexyphenidyl, morphine sulfate, and acetaminophen.

A neurologic consultant's evaluation on the day of transfer revealed no sensory or motor deficit and mild signs of Parkinson's disease consisting of masking and a decreased blink rate. The carbidopa/levodopa and the trihexyphenidyl were discontinued in order to eliminate their possible hemodynamic effects. Over the subsequent five preoperative hospital days successive neurologic examinations revealed increasing clinical signs of active Parkinson's disease such as increased masking, positive glabellar sign, and a fine tremor. No muscular rigidity was detected.

Cardiac catheterization performed on the 2nd day after admission showed severe three-vessel coronary artery occlusive disease with a large anterolateral and apical left ventricular aneurysm and a mural thrombus. There was no clinical evidence of embolic phenomena preoperatively. Serum electrolyte levels were consistently normal with potassium ($K^+$) ranging from 4.0 to 4.4 meq/L. Serial electrocardiograms (ECG) and serum enzyme levels showed an evolving extensive anterior myocardial infarction. Chest x-rays consistently showed interstitial pulmonary edema. Serial arterial blood gases were notable only for mild relative hypoxemia. Other laboratory studies were noncontributory.

On the 6th day after admission, the patient was brought to the operating room for a triple coronary artery bypass graft and a left ventricular aneurysmectomy. No premedication was given. Arterial blood gas tensions (ABGs) and serum electrolyte levels before induction of anesthesia are shown in the Table. After preinduction administration of 1 mg of pancuronium, anesthesia was induced with diazepam (30 mg IV) over 5 minutes, morphine sulfate (75 mg) as a continuous infusion over 20 minutes, and nitrous oxide (4 L/min) with oxygen (4 L/min). A continuous infusion of succinylcholine (800 mg over 30 minutes) and a nitroglycerin infusion (50 μg/min) were also given. The patient remained hemodynamically stable throughout induction with a regular sinus rhythm at a rate of 70 to 80/min, arterial pressure with counterpulsation of 100/125/45 mm Hg, pulmonary artery pressure 16/11 ± 2 mm Hg, CVP 5 ± 1 mm Hg, and ST segments unchanged from preinduction baseline in leads II or $V_4$. The hemodynamic response to endotracheal intubation was minimal. During the surgical preparation of the skin, however, pressures increased to 125/150/55 mm Hg (arterial), 44/22 mm Hg (PA), and 21 mm Hg (PCW). Widening of the QRS complexes, increased ST segment elevation in $V_4$, and new ST segment depression in lead II were noted. Blood samples for ABGs and electrolyte levels were sent to the laboratory. In response to the above changes, an additional 45 mg of morphine sulfate and 30 mg of d-tubocurarine were given, the succinylcholine infusion was discontinued, the nitroglycerin infusion was increased, and a nitroprusside infusion was started. This resulted in resolution of the hemodynamic and new ST segment disturbances. Serial serum electrolyte levels and ABGs, are summarized in the Table, revealed marked hyperkalemia to 7.6 meq/L following intubation. All serum electrolyte determinations were made using arterial blood after clearing the arterial line of any flush solution.

Subsequent precardiopulmonary bypass (CPB) and CPB course were unremarkable. Termination of CPB was accom-

---

* Instructor in Anaesthesia, Harvard Medical School; Assistant in Anesthesia, Massachusetts General Hospital.

Received from the Department of Anesthesia, Bowman Gray School of Medicine, 300 S. Hawthorne Road, Winston-Salem, North Carolina 27103. Accepted for publication January 28, 1980.

**TABLE**
**Arterial Blood Gas Tensions and Serum Electrolyte Levels**

| Time | Status of procedure | Succinylcholine infusion | Ventilation | $F_{I_{O_2}}$ | $Pa_{O_2}$ | $Pa_{CO_2}$ | pH | Base excess | $Na^+$ | $K^+$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *torr* | *torr* | | *mmole/L* | *meq/L* | *meq/L* |
| 10:45 a.m. | Before induction | Off | Spontaneous | 0.4 | 154 | 43 | 7.41 | +2 | 136 | 4.2 |
| 11:20 a.m. | After intubation | On | Hand ventilated | 0.5 | 151 | 45 | 7.37 | 0 | 126 | 7.6 |
| 11:30 a.m. | After incision | Off | Hand ventilated | 0.5 | 175 | 51 | 7.29 | −3 | 126 | 6.0 |
| 12:05 p.m. | Cannulation | Off | Hand ventilated | 0.5 | 273 | 33 | 7.44 | −1 | 127 | 3.9 |

plished with two doses of intravenous calcium chloride (200 mg each), an infusion of epinephrine (2.5 μg/min), and continued balloon counterpulsation.

The postoperative course was complicated by refractory ventricular ectopy. Otherwise, hemodynamic stability quickly ensued such that the epinephrine infusion could be decreased and then discontinued over the next 12 hours. No new myocardial ischemia was evident from either postoperative ECGs or serum CPK-MB levels. There were no postoperative acid-base or electrolyte disturbances of note. Extubation was accomplished 18 hours postoperatively. Anti-Parkinson medications were resumed on the 8th postoperative day, by which time a full-blown Parkinson's syndrome was evident including rigidity and cog-wheeling. The patient was discharged in good condition on the 16th postoperative day.

## Discussion

The complexity of this patient's cardiovascular status made it somewhat difficult to analyze the etiology of the hyperkalemia. Fortunately, the hyperkalemia was of no clinical consequence and resolved spontaneously. The increased duration of the QRS interval during the hyperkalemic period could have been caused by an ischemia-induced conduction delay. It was surprising that hyperkalemia of this magnitude did not cause a more significant disturbance in conduction.

Several differential diagnoses were entertained in an effort to explain the hyperkalemia: (1) laboratory error; (2) intravascular massive hemolysis or a hemolyzed blood sample; (3) metabolic acidosis (low cardial output or malignant hyperpyrexia); (4) iatrogenic potassium overdose; and (5) succinylcholine-induced hyperkalemia (based on either unrecognized denervated muscle and/or secondary to Parkinson's disease). Laboratory error was unlikely in view of the time course of the hyperkalemia, its rapid resolution, and the fact that repeated measurements of serum $K^+$ in the hyperkalemic sample after a calibration check by the laboratory technician confirmed the elevation of $K^+$ levels. The presence of intravascular foreign bodies in the form of the balloon and a mural thrombus would predispose to hemolysis, but the laboratory reported that the serum contained no free hemoglobin. The ABGs showed that metabolic acidosis was not present to any significant degree at the time hyperkalemia was present although the variability of "the educated hand" was well demonstrated by fluctuations in the respiratory acid-base status. There was no evidence of malignant hyperpyrexia. All intravenous infusions and injections were checked to assure that no potassium had inadvertently been given. No blood or plasma had been given up to this time, and the only potassium solution administered was lactated Ringer's solution in the amount of about 250 ml during induction. Multiple factors predisposed this patient to unrecognized upper and lower motor neuron deficits including a left ventricular mural thrombus (cerebral embolus risk), lumbar laminectomies for lumbar disc disease, and poorly controlled Parkinson's disease. Daily neurologic examinations (as recent as 12 hours preoperatively) failed to reveal any motor deficit whatsoever. Signs of parkinsonism were on the increase in the five preoperative days during which his anti-Parkinson medications had been discontinued.

A computer search of the literature dating backward to the early 1960s revealed no report of succinylcholine-induced hyperkalemia in a patient with Parkinson's disease. Cooperman[1] evaluated increases in potassium levels after succinylcholine in 32 patients with various neuromuscular diseases. Patients with Parkinson's disease were included in his study among a group of nine patients with either multiple sclerosis, Parkinson's disease, or muscular dystrophy. The number of patients who had Parkinson's disease, their neurologic state, and their medical therapy were not specifically mentioned. Of the 15 reported hyperkalemic responses to succinylcholine, no such reaction was reported in a patient with Parkinson's disease.[2]

Other reports[3-6] addressing the management of anesthesia for the patient with Parkinson's disease have dealt primarily with the anesthetic implications of levodopa therapy. No reference was made to the use of neuromuscular blocking agents in patients with Parkinson's disease. Because parkinsonian rigidity is theoretically based on upper motor neuron pathology (perhaps in facilitory-inhibitory modulators of upper motor neurons), it would seem quite feasible that succinylcholine might induce hyperkalemia in these patients.

The anesthetic technique used in this patient might be criticized for the excessive dose of succinylcholine used. Succinylcholine infusions are commonly used in this institution during the induction of anesthesia in hemodynamically unstable cardiac surgical patients. It is chosen for its lack of hemodynamic disturbance, and little heed is paid to traditional dose titration because phase II block is of no consequence in these patients. In any event, succinylcholine-induced hyperkalemia is not dose-related in a clinically significant manner.

In summary, a case has been presented in which succinylcholine-induced hyperkalemia occurred in a patient with poorly controlled Parkinson's disease. No inference can be made regarding the risk of occurrence of this phenomenon in patients with Parkinson's disease under good medical control. Anesthesiologists are advised to consider this case report when planning general anesthesia for patients with Parkinson's disease.

## ACKNOWLEDGMENT

The author thanks Dr. John J. Savarese for his constructive comments in reviewing the manuscript.

## REFERENCES

1. Cooperman LH: Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA 213:1867-1871, 1970
2. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89-99, 1975
3. Ngai SH: Parkinsonism, levodopa, and anesthesia. Anesthesiology 37:344-351, 1972
4. Bevan DR, Monks PS, Calne DB: Cardiovascular reactions to anaesthesia during treatment with levodopa. Anaesthesia 28: 29-31, 1973
5. Greenhouse AH: Anesthesia in the parkinsonian on levodopa. Rocky Mt Med J 68:60-62, 1971
6. Rivera VM, Keichian AH, Oliver RE: Persistent parkinsonism following neuroleptanalgesia. Anesthesiology 42:635-637, 1975
7. Katz J, Kadis LB: Anesthesia and Uncommon Diseases. WB Saunders Co, Philadelphia, 1973, pp 385-386

---

## Relief of Dental Pain by Ice Massage of the Hand

Patients suffering from acute dental pain were treated with ice massage of the web between the thumb and index finger of the hand on the same side as the painful region. Control groups received tactile massage alone or with explicit suggestion that the massage was intended to alleviate their pain. Changes in pain intensity produced by the procedures were measured with the McGill Pain Questionnaire. Ice massage decreased the intensity of the dental pain by 50% or more in the majority of patients. Furthermore, the pain reductions produced by ice massage were significantly larger than those produced by tactile massage alone or with explicit suggestion. The results indicate that ice massage has pain-reducing effects comparable to those of transcutaneous electrical stimulation and acupuncture. The fact that cold signals are transmitted to the spinal cord exclusively by A-$\delta$ fibers and not by C fibers provides a potential method for differentiating the various feedback systems that mediate analgesia produced by different forms of intense sensory input. Ice massage provides a simple method for the palliative control of dental pain. *(Melzack R, Guité S, Gonshor A: Relief of dental pain by ice massage of the hand. Can Med Assoc J 122:189–191, 1980)*

ANESTH ANALG
59:447-451, 1980

# Prolonged Neural Blockade following Regional Analgesia with 2-Chloroprocaine

**Ram S. Ravindran, MD,***
**Virginia K. Bond, MD,***
**Mark D. Tasch, MD,†**
**Chakrapani D. Gupta, MD,†**
**and Thomas G. Luerssen, MD‡**

Serious neurologic complications occasionally associated with epidural or spinal anesthesia include anterior spinal artery syndrome, transverse myelitis, cauda equina syndrome, and chronic arachnoiditis.[1] In most of the reported cases the exact etiology cannot be identified. In addition, neurologic deficits can occur spontaneously in the absence of anesthesia[2] or following general anesthesia.[3]

The most frequent cause of neurologic deficits involving the spinal cord after surgery with either regional or general anesthesia is an anterior spinal artery spasm or thrombosis. The resulting anterior spinal artery syndrome is characterized by motor paralysis with preservation of touch, pressure, vibration, and proprioception senses.[4] It is usually a clinical diagnosis made in the presence of negative myelographic findings. Most cases of anterior spinal artery syndrome have resulted from surgery involving the abdominal aorta or lumbar vessels. Usubiaga[5] reported ten cases of anterior spinal artery syndrome in patients who had epidural analgesia for surgery not involving the aorta or vertebral column. In his series most of the patients were more than 45 years old, epinephrine was used in the anesthetic mixture, the anesthetic course was marked by one or more hypotensive episodes, and none of the patients recovered neurologic function. In contrast, patients with a cauda equina syndrome following spinal or epidural anesthesia may experience some degree of recovery.[6]

The present report describes two patients with signs and symptoms suggestive of both anterior spinal artery and cauda equina syndromes following epidural analgesia and one patient with similar symptoms after an inadvertent subarachnoid injection. All three patients received 2-chloroprocaine specifically prepared for use in caudal and epidural anesthesia.

## Case Reports

### Case 1

A 34-year-old, 70 kg, 158-cm tall gravida 4 para 3 white woman was admitted to the hospital for labor and delivery. Previous deliveries had been accomplished without regional analgesia. She had received local anesthetics for dental surgery without complications. Vital signs included blood pressure 120/80 torr, heart rate 90 beats per minute, and respiratory rate 18/min. When the cervix was 4 cm dilated and contractions were 2 to 3 minutes apart it was decided to place a catheter in the lumbar epidural space to provide analgesia. Lactated Ringer's solution (500 ml) with 5% dextrose was given intravenously. With the patient in the left lateral position the back was prepared with Merthiolate solution and wiped clean. Using the loss of resistance technique a 17-gauge Tuohy needle was placed in the epidural space at the L3-L4 interspace. Preservative-free saline was used for identification of the epidural space. A 19-guage epidural catheter was introduced through the needle without difficulty. Neither blood nor cerebrospinal fluid could be aspirated. Three milliliters of 3% 2-chloroprocaine was injected through the epidural catheter. No paresthesia was elicited on placement of the needle, catheter, or injection of local anesthetic. About 2 minutes later the patient stated that her left lower extremity was numb but that she could move it. There was no analgesia in the right lower extremity. Hypalgesia extended to the T-12 level on the left. Blood pressure remained stable at 110/80 torr. The patient was relieved of labor pains for about 20 minutes but then again experienced abdominal discomfort with uterine contractions. Another 3 ml of 3% 2-chloroprocaine was injected. This resulted in a bilateral band of anesthesia extending from T-8 to L-1. The patient could move both legs but continued to have numbness in the left lower extremity while the right lower extremity was not numb in areas innervated by nerve roots below L-1. Blood pressure remained stable at 100/70 torr. Ninety minutes following the second injection the patient was taken to the delivery room. There was no perineal analgesia at this time and hence 10 ml of 3% 2-chloroprocaine was injected. Within 2 minutes of injection the patient had good perineal analgesia. The upper level of analgesia was T-4. She complained of shortness of breath and was given supplemental oxygen. Clinically tidal volume appeared adequate. Blood pressure remained stable at 100 to 110/70 to 80 torr. Fetal heart rate

---

* Assistant Professor, Department of Anesthesia.

† Anesthesia Resident, Department of Anesthesia.

‡ Chief Resident, Department of Neurosurgery.

Received from the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, IN 46202. Accepted for publication February 25, 1980.

Reprint requests to Dr. Ravindran.

was within normal limits. Delivery was accomplished with outlet forceps. The patient remained conscious and able to talk throughout delivery. The infant's Apgar scores were 7 and 9 at 1 and 5 minutes, respectively.

In the recovery room the sensory level regressed from T4 to L1 within 2 hours. She could dorsiflex her right toes but could not flex, abduct, or adduct her right hip, or flex her right knee or ankle. She could move no part of her left lower extremity. Ten hours later, because of the patient's unchanging neurologic status, a neurologic consultation was obtained. An emergency myelogram to exclude spinal cord compression from prolapsed lumbar disc or extradural hematoma was interpreted as normal. The cerebrospinal fluid pressure was normal and the fluid was slightly blood-tinged. Corrected white cell count was 3 cells/mm.[3] Chemical analysis of spinal fluid revealed protein content of 225 mg/dl and sugar 45 mg/dl. Smear and culture of spinal fluid were negative for bacteria. Pressure, touch, vibration, and proprioception were intact in both lower extremities. Tactile discrimination and temperature sensations were bilaterally absent below L-1. The knee and plantar reflexes were absent bilaterally. The patient could not void even though she felt bladder distention. The neurologist's diagnosis was anterior spinal artery spasm or thrombosis.

Analysis in our laboratory of the cerebrospinal fluid obtained 16 hours following the delivery revealed the presence of 2-chloroprocaine. Quantitative analysis could not be done. On the second postpartum day the patient's plasma pseudocholinesterase level was 7.6 units (7 to 19 units normal). The dibucaine number was 75%. Analysis of dialyzed cerebrospinal fluid revealed the protein concentration to be 150 mg/dl (2-chloroprocaine gives a positive reaction for protein). Analysis of the venous plasma obtained 16 hours following delivery also revealed a detectable amount of 2-chloroprocaine.

Since there was direct and indirect evidence of drug in the cerebrospinal fluid and in the plasma the patient was given 2 units of type-specific fresh plasma to hasten hydrolysis of the drug in the plasma and thus removal of the drug from the cerebrospinal fluid. In addition 25 gm of mannitol and 2000 ml of lactated Ringer's solution was administered to establish diuresis and speed drug elimination via the kidneys. On the third postpartum day 2-chloroprocaine in the venous plasma could not be detected. Diuresis and fluid administration were continued for two more days. On the seventh postpartum day analysis of the cerebrospinal fluid and venous plasma revealed no detectable 2-chloroprocaine. Cerebrospinal fluid protein was 150 mg/dl and sugar 50 mg/dl. The patient's serum was also found to hydrolyze a known quantity of 2-chloroprocaine within 2 minutes. Reanalysis at the Pennwalt laboratory of plasma and cerebrospinal fluid obtained 16 hours following delivery revealed insignificant amounts of the drug.

On the fifth postpartum day the patient could slightly adduct at the right hip joint. Over the next 6 days she was able to flex her right thigh at the hip and leg at the knee. She could not move any part of her left lower extremity. On the seventh postpartum day electromyography studies were recommended[7] but the patient declined.

Computed tomography of the spinal cord revealed no abnormalities. Selective angiography to delineate the spinal arterial tree was considered too risky at the time, as the procedure itself has been reported to cause anterior spinal artery spasm.[8] On the 14th postpartum day the patient was transferred to the spinal cord unit for intensive physical therapy. She gradually regained moderate strength in both lower extremities, sooner in the right leg than in the left. Four weeks following epidural analgesia the patient could move her right leg with ease and was able to flex, abduct, and extend at her left hip, to dorsiflex her left toes, and to walk with the aid of crutches and braces on the left leg. She had control of bladder and rectal sphincters. Ankle jerks were present bilaterally.

## Case 2

An 18-year-old, 68 kg, 160-cm tall, gravida 2 para 1 white woman was admitted to the hospital for labor and delivery. She had received a bupivacaine continuous epidural anesthesia for her previous delivery and desired epidural analgesia for the present delivery. Vital signs included blood pressure 110/70 torr, heart rate 90 beats per minute, and respiratory rate 20/min. When the cervix was 5 cm dilated it was decided to place a lumbar epidural catheter to provide analgesia. Lactated Ringer's solution (500 ml) with 5% dextrose was given intravenously. With the patient lying in the left lateral position the back was cleansed with Merthiolate solution and wiped clean. Using the loss of resistance technique, a 17-gauge Tuohy needle was introduced into the epidural space at the L3-L4 interspace. A 19-gauge epidural catheter was placed without difficulty. Neither blood nor cerebrospinal fluid could be aspirated. A test dose of 3 ml of 0.5% bupivacaine with 1:200,000 epinephrine was injected. A band of sensory hypalgesia extending from T-8 to L-1 developed with no motor weakness of the lower extremities.

The blood pressure was stable at 106 to 112/70 to 80 torr. A second injection of 8 ml of 0.5% bupivacaine with epinephrine 45 minutes later produced sensory anesthesia and motor paralysis in lower extremities in 2 minutes. Again, neither blood nor cerebrospinal fluid could be aspirated through the catheter. Systolic blood pressure remained stable at 100 to 110 torr. Two hours following the second injection the patient was taken to the delivery room. The epidural catheter was withdrawn 1 cm and again aspiration was negative. Since there was no perineal analgesia 12 ml of 3% 2-chloroprocaine was injected. The patient felt immediate relief of pain. Sensory anesthesia and motor block extended bilaterally to T-4. Systolic blood pressure decreased to 90 from 100 torr. The uterus was quickly displaced to the left and 500 ml of lactated Ringer's solution with 5% dextrose was administered intravenously together with ephedrine, 15 mg. Blood pressure increased to 110/70 torr. The patient continued to ventilate adequately. Delivery was rapidly accomplished with outlet forceps application. The infant had Apgar scores of 6 and 9 at 1 and 5 minutes, respectively.

In the 3 hours following delivery the motor and sensory levels of anesthesia regressed to T-12 but after 8 hours the patient could barely move her toes. Touch, vibration, pressure, and proprioception sensations were normal over both the lower extremities. It was speculated at this time that prolonged anesthesia had resulted from epinephrine administered with the bupivacaine. After 28 hours she could flex her right leg at the knee but knee and ankle jerks were absent bilaterally and she could not void. The rectal sphincter had no tone. Forty hours after delivery she could move both lower extremities but they were weak. She completely recovered and neurologic examination was entirely normal 72 hours after delivery.

### Case 3

A 29-year-old, 60 kg, 160-cm tall, gravida 2 para 1 white woman, who had delivered under saddle block with lidocaine the previous day, desired epidural analgesia for bilateral tubal ligation. With the patient lying in the left lateral position, using the loss of resistance technique, a 17-gauge Tuohy needle was placed in the epidural space via the L3-L4 interspace without any difficulty. Neither blood nor cerebrospinal fluid could be aspirated through the catheter. A test dose of 4 ml of 2% 2-chloroprocaine produced no sensory analgesia after 4 minutes. Therefore 23 ml of 2% 2-chloroprocaine was injected. This was rapidly followed by a sensation of generalized warmth followed by dyspnea which progressed to apnea. Artificial ventilation with oxygen was instituted and the patient placed in moderate Trendelenburg position since 2% 2-chloroprocaine is hypobaric. The diagnosis was inadvertent subarachnoid injection. Vital signs remained stable. The sensory level regressed to T-10 after 2.5 hours, at which time tidal volume and vital capacity were considered normal. Five hours later she felt tingling sensations in her right lower extremity but could move neither lower extremity. After 16 hours she could walk with assistance. She was released from the hospital 72 hours postoperatively with residual numbness in both heels and both buttocks. These symptoms subsided over 6 months.

## Discussion

In a recent review of large series of spinal and epidural techniques[9–11] Abouleish[12] categorically stated that, following epidural and spinal analgesia, neurologic problems should not occur if patient selection, medication, and anesthetic technique are all properly managed. Usubiaga,[5] after reviewing the world literature, concluded that serious neurologic problems associated with major regional anesthesia are rare but can occur in one in 10,000 cases following either epidural or spinal analgesia. Despite the rarity of neurologic complications after regional anesthesia, as emphasized by these reports, we observed three patients with a neurologic deficit within an 18-month period. Nearly 2000 regional anesthetics were administered during that period.

Neurologic complications following epidural or spinal analgesia can result from anesthesia, surgery, or exacerbation of preexisting disease. Neurologic complications associated with the anesthesia itself can result from accidental injection of neurolytic agents, including antiseptic solutions, from trauma due to inappropriate manipulation of needles, from bacteriologic infections, from arterial hypotension, and from hematomas.[5] In our three cases standard anesthetic techniques and medications were used. In fact, the 3% 2-chloroprocaine that was used in case 1 was drawn up into different syringes from the same vial, and one of the syringes was used for epidural analgesia for another patient. Anesthesia lasted the expected 2 hours in this other patient.

The three cases described in this report have in common the use of 2-chloroprocaine (2% or 3%). In cases 1 and 2 the anesthetic course was typical of epidural analgesia. The only evidence of possible subarachnoid injection was the rather rapid onset of perineal analgesia in both cases following injection of 10 and 12 ml of 3% 2-chloroprocaine. However, in our experience inadvertent injection into the subarachnoid space of only 3 ml of 3% 2-chloroprocaine results in development of near total spinal analgesia. It is further unlikely that the anesthetic injected through the epidural catheter in cases 1 and 2 entered the subarachnoid space since neither patient developed respiratory difficulty or hypotension.

2-Chloroprocaine is widely used to provide epidural analgesia because of its short latency, low toxicity, short duration of action, and minimal transplacental transfer to the fetus. 2-Chloroprocaine is recommended for use in infiltration, caudal, and epidural analgesia. It is our understanding that the Food and Drug Administration has not approved the use of 2-chloroprocaine for subarachnoid injection. The failure to seek FDA approval for subarachnoid use may be related to the absence of any apparent advantage of 2-chloroprocaine over other widely used drugs already approved for spinal anesthesia. Nevertheless, Foldes and McNall,[13] in 1952, used 3.3% 2-chloroprocaine for spinal analgesia without any adverse effects. Collins[14] feels that 4% 2-chloroprocaine, being hyperbaric, is better than 3.3% for spinal analgesia.

The possibility of chloroprocaine causing vascular spasm or neurotoxicity in the spinal subarachnoid space deserves investigation, as even in expert hands inadvertent subarachnoid entry occurs in about one in 50 cases[15] and perhaps as often as one in 10 or 20 cases in less experienced hands.[16] Furthermore, one of the mechanisms of action of epidural anesthetics is penetration through the dural cuff surrounding the nerve roots or directly through the dura into the subarachnoid space.[17, 18] If 2-chloroprocaine is potentially hazardous in the subarachnoid space should it be used for epidural anesthesia?

Inadvertent subarachnoid injection of small amounts (3 ml) of 2-chloroprocaine during attempted epidural anesthesia has not produced any adverse effects in a patient known to one of the authors (R.S.R.) even though it resulted in total spinal analgesia. Kim et al[19] reported a case in which inadvertent injection of 2.5 ml of 2% 2-chloroprocaine resulted in total spinal analgesia and hemicranial palsy. The patient recovered completely in 12 hours. We have been unable to find reports of prolonged neural blockade following epidural analgesia with 2-chloroprocaine comparable to that reported with bupivacaine.[20] Furthermore we are unaware of any reports describing inadvertent injection of large volumes of 2-chloroprocaine into the subarachnoid space which resulted in prolonged blockade.

Are there any physicochemical or pharmacologic properties that are unique to 2-chloroprocaine that might possibly cause prolonged neural blockade? There are two physicochemical properties unique to 2-chloroprocaine: (1) 3% 2-chloroprocaine is nearly hyperbaric at 37 C[19]; (2) 2% and 3% 2-chloroprocaine have a pH of 2.7 to 4.0.[21] Other local anesthetics made hyperbaric by mixing with 10% dextrose solution are routinely used to provide spinal anesthesia without adverse effects; however, they are used in very small volumes. If larger volumes of hyperbaric solutions were to be injected into the subarachnoid space, as can occur following an inadvertent subarachnoid injection of 2-chloroprocaine, then it might affect the conductive properties of the nerve root by its osmotic effects. Concentrated local anesthetics, by virtue of their osmotic effects, have been speculated to cause neurotoxicity.[22] Covino and Vassallo[23] have observed vasculitis in some cases following intravascular injection of 2-chloroprocaine and therefore do not recommend its use for intravenous regional analgesia. Acidic solutions might irritate the nerve roots or meninges or cause vasospasm. If 2-chloroprocaine is injected in small amounts it may be diluted in the subarachnoid fluid and therefore may not produce adverse effects. This may be why we have not seen prolonged neurologic dysfunction following inadvertent subarachnoid injection of small volumes of 2-chloroprocaine.

In summary, we report three cases of prolonged neural blockade following major regional analgesia with 2-chloroprocaine. These three cases were initially thought to be anterior spinal artery syndrome on the basis of preservation of posterior tract functions. However, subsequent regression or complete return of normal neurologic function is more suggestive of the cauda equina syndrome.

In Case 1, until the normal hydrolysis of 2-chloroprocaine by the patient's serum was documented, a slim possibility of atypical pseudocholinesterase as the etiology of prolonged analgesia was entertained, though a recent report[24] indicates that it is an unlikely cause.

Within the last month we have also received enquiries from two anesthesiologists concerning similar prolonged neurologic dysfunction occurring in two of their patients following inadvertent subarachnoid injection of large volumes of 2-chloroprocaine. Based on these personal communications and on the experience gained with our three patients we feel that a test dose before injection of large volume of 2-chloroprocaine is mandatory to rule out subarachnoid injection. 2-Chloroprocaine should not be injected if there is any possibility of its being injected into the subarachnoid space. Even with these precautions we remain concerned about the prolonged neurologic deficit following an apparently uneventful epidural anesthetic without subarachnoid entry (case 1).

## ADDENDUM

The Pennwalt Corporation analyzed samples from the three lots of medication used on these patients and found them to meet their specifications.

## REFERENCES

1. Wylie WD, Churchill-Davidson HC: A Practice of Anaesthesia. Third edition. Chicago, Year Book Medical Publishers, Inc, 1971, pp 1236–1242
2. Crawford JS: Pathology in the epidural space. Br J Anaesth 47: 415–417, 1975
3. Ciliberti BJ: Paraplegia following inhalation anesthesia for subtotal gastrectomy: a case report. Anesthesiology 9:439–440, 1948
4. Baker AB, Baker LH: Clinical Neurology. New York, Harper and Row, 1978, Volume 3, pp 12–13
5. Usubiaga J: Neurological complications following epidural anesthesia. Int Anesthesiol Clin 3:69–75, 1975
6. Searles PW, Nowill WK: The role of sterilizing solutions in the cauda equina syndrome following spinal anesthesia. NY State J Med 50:2541–2544, 1956
7. Marinacci AA, Courville CB: Electromyogram in evaluation of neurological complications of spinal anesthesia. JAMA 168: 1337–1345, 1958

8. McCormack JG: Paraplegia secondary to abdominal aortography. JAMA 61:860–862, 1956
9. Phillips OC, Ebner H, Nelson AT, et al: Neurologic complications follwing spinal anesthesia with lidocaine. Anesthesiology 30:284–289, 1969
10. Bonica JJ: Peridural block: analysis of 3,637 cases and a review. Anesthesiology 18:723–745, 1957
11. Dripps RD, Vandam LD: Long term follow up of patients who received 10,098 spinal anesthetics. JAMA 156:1486–1490, 1954
12. Abouleish E: Pain Control in Obstetrics. Philadelphia, JB Lippincott Co, 1977, pp 292–293
13. Foldes FF, McNall PG: 2-Chloroprocaine: A new local anesthetic agent. Anesthesiology 13:287–296, 1952
14. Collins JJ: Principles of Anesthesiology. Second edition. Philadelphia, Lea & Febiger, 1976, pp 876–877
15. Dawkins CJ: An analysis of the complications of extradural and caudal block. Anaesthesia 24:554–563, 1969
16. Crawford, JS: Lumbar epidural block in labor: a clinical analysis. Br J Anaesth 44:66–74, 1972
17. Bromage PR: Epidural Analgesia. Philadelphia, WB Saunders & Co, 978, pp 119–135
18. Usubiaga, JE, Wikinski J, Wikinski R, et al: Transfer of local anesthetics to the subarachnoid space and mechanisms of epidural block. Anesthesiology 25: 752–759, 1964
19. Kim YI, Mazza NM, Marx GF: Massive spinal block with hemicranial palsy after a "test dose" for extradural analgesia. Anesthesiology 43:370–372, 1975
20. Pathy GV, Rosen M: Prolonged block with recovery after extradural analgesia for labor. Br J Anaesth 47: 520–522, 1975
21. Nesacaine (chloroprocaine hydrochloride) Product Monograph. Rochester, NY, Pennwalt Pharmaceutical Division
22. Noble AB, Murray JG: A review of the complications of spinal anaesthesia with experiences in Canadian teaching hospitals from 1959 to 1969. Can Anaesth Soc J 18:5–15, 1971
23. Covino B, Vassallo J: Local Anesthetics. New York, Grune & Stratton, 1976, pp 67–68
24. Zsigmond EK, Hinsvark ON, Chandra P, et al: Pharmacokinetics of 2-chloroprocaine in $E_1^aE_1^a$. Anesthesiology 51:S222–S223, 979

---

## Nitroprusside Effects on Blood Volume and Venous Return

The effects of nitroprusside (380 to 760 μg/min) on the systemic venous return, the central blood volume, and the equilibrium point between the venous return and cardiac output curves were studied in eight dogs using a right-heart bypass preparation at constant total blood volume. Experiments were performed before and after the production of acute left ventricular failure. During the control period, nitroprusside infusion shifted the venous return curve, with a reduction in its plateau (3.1 to 2.4 L/min; $p < 0.005$), the central blood volume fell (−2.4 ± 0.4 ml/kg; $p < 0.05$) and the cardiac output at equilibrium was reduced (3.1 to 2.4 L/min; $p < 0.005$). Cardiac failure, produced by acute coronary artery ligation, increased the central blood volume (+6.3 ± 0.5 ml/kg; $p < 0.01$), leading to a decrease in both the systemic blood volume and the plateau of the venous return curve (3.2 to 2.6 L/min; $p < 0.003$). The cardiac output at equilibrium was also reduced (3.2 to 1.9 L/min; $p < 0.001$). In this setting, nitroprusside infusion decreased the central blood volume (−7.4 ml/kg; $p < 0.01$), but the venous return curve was not altered. The cardiac output curve was markedly shifted upward due to reduced afterload on the failing left ventricle; however, in the absence of a downward shift of the venous return curve, the cardiac output at equilibrium increased from 1.9 to 2.6 L/min; $p < 0.05$). The authors conclude that the differing effects of nitroprusside in acute cardiac failure are due primarily to an increased shift of blood from the central circulation in the failure state compared with the normal circulation. This shift counteracts the systemic venodilation produced by nitroprusside and allows the markedly improved left ventricular function consequent to reduced afterload to be expressed as increased venous return and cardiac output. *(Pouleur H, Covell JW, Ross J Jr: Effects of nitroprusside on venous return and central blood volume in the absence and presence of acute heart failure. Circulation 61:328–337, 1980)*

ANESTH ANALG
59:452-454. 1980

# Persistent Neurologic Deficit and Adhesive Arachnoiditis following Intrathecal 2-Chloroprocaine Injection

**Laurence S. Reisner, MD,***
**Bruce N. Hochman, MD,† and**
**Michael H. Plumer, MD***

Because of its apparent broad margin of safety 2-chloroprocaine has become widely used, especially for epidural analgesia in obstetrics. Other advantages are rapid onset, short duration of action, rapid hydrolysis by plasma cholinesterase in both mother and fetus, and little if any detectable fetal effect. Additionally it is suggested that inadvertent subarachnoid injection of 2-chloroprocaine would produce a blockade of lesser degree and duration than other local anesthetics.[1] However, the following case report documents total spinal anesthesia followed by prolonged neurologic impairment after an inadvertent subarachnoid injection of a full epidural dose of 3% 2-chloroprocaine. This patient's course was further complicated by the development of adhesive arachnoiditis.

## Case Report

A 33-year-old Mexican-American woman, gravida 4 para 4, was scheduled for an elective postpartum tubal ligation under epidural anesthesia. She was 61 inches (155 cm) tall and weighed 130 lb (59 kg). The patient's medical history was significant only in that she had undergone an appendectomy 4 years previously under spinal anesthesia with 10 mg of tetracaine without incident. In the operating room routine monitoring devices were applied and an intravenous infusion begun. A fluid load of 1000 ml of 5% dextrose in lactated Ringer's solution was administered. Her blood pressure was 120/80 torr and her pulse rate 80 beats per minute. The patient was placed in the left lateral decubitus position and after the back had been washed with 70% isopropyl alcohol tinted with methylene blue, sterile drapes were applied and the skin over the second lumbar interspace infiltrated with 1 ml of 3% 2-chloroprocaine (3% Nesacaine-CE, Pennwalt Pharmaceutical Division, Pennwalt Corporation). An 18-gauge disposable Crawford needle (Monoject no. 221, Sherwood Medical Industries) was advanced into the epidural space utilizing a loss-of-resistance technique. This required several attempts as the patient was quite anxious and mobile. No paresthesia was observed, and aspiration yielded neither blood nor cerebrospinal fluid. A 3-ml test dose of 3% 2-chloroprocaine without preservatives containing 5 $\mu$g/ml of freshly added epinephrine (final concentration 1:200,000) produced no evidence of subarachnoid or intravenous placement over a 3-minute observation period. An additional 25 ml of the same solution was then injected and the needle removed. The patient was placed in the supine position, and within 30 seconds she had difficulty breathing and could speak only in a whisper. Her ventilation was first assisted and then controlled by bag and mask with 100% oxygen. Blood pressure and pulse rate remained unchanged, and endotracheal intubation was performed after administration of 20 mg of succinylcholine to ensure adequate conditions. Blood pressure and pulse remaining stable, the operation was completed with amnesia produced by 20 mg of ketamine and 50% nitrous oxide in oxygen with controlled ventilation.

She was taken to the recovery room in stable condition but still completely paralyzed. A total of 5½ hours of mechanical ventilation was required before the endotracheal tube could be removed. The first motor effort was movement of her right eyelid 3 hours after the anesthetic, followed by diaphragmatic respiratory efforts by 4½ hours. At the time of extubation she was alert and orientated but a sensory level to pinprick at the sixth thoracic dermatome persisted. Motor function of the upper extremities was good but she was unable to move her legs.

Twenty hours after the block the sensory level was still at T-12 with marked weakness of the lower extremities. Twenty-five hours after injection she had an S-2 sensory level with continued lower extremity weakness. In addition she complained of a headache when placed in the upright position. Vibratory and position senses were intact at this time. Because of persistent sensory and motor deficits neurologic and neurosurgical consultations were obtained 30 hours after the initial block. Myelography was not performed because the symptoms did not suggest a mass lesion and because the procedure itself carries a small but finite risk of inducing arachnoiditis.

Thirty-six hours after injection she could flex her legs at the knee. Physical therapy was begun and by the 7th day the patient could walk but only with substantial assistance. An electromyogram (EMG) with H-reflex studies showed no abnormality through the first sacral segment. By the 14th

---

* Associate Clinical Professor, Anesthesiology and Reproductive Medicine.

† Resident in Anesthesiology.

Received from the Department of Anesthesiology, University of California Medical Center, San Diego, 225 Dickinson St., San Diego, California 92103. Accepted for publication March 3, 1980.

Reprint requests to Dr. Reisner.

day she could walk with minimal assistance, but she was incontinent of feces and had no urge or ability to void. She regained normal bowel control at the end of the 3rd week, and marked improvement in lower extremity function was evident. A cystometrogram showed an urge to void and sensation of fullness at normal volumes but weak detrusor activity. She could discriminate between warm and cool fluid instillations but could not void either voluntarily or by reflex action. Four weeks after her anesthetic, the patient was discharged. Although she could walk and ascend and descend a flight of stairs carrying her infant, she required intermittent bladder catheterization and had a persistent S-4 sensory level to pinprick.

Seven weeks after the initial incident, she was readmitted to the hospital complaining of back pain, loss of lower extremity function, and loss of sensation in her legs and buttocks. Examination revealed marked paresis of the lower extremities and patchy sensory loss to T-12. An EMG now revealed changes consistent with new and old cauda equina injury. An H-reflex was present on the left side but not on the right. A myelogram utilizing metrizamide (Amipaque, Nyegaard and Co.) as the contrast medium was consistent with a diagnosis of adhesive arachnoiditis. The greatest involvement was in the lumbosacral and the thoracolumbar regions. Also consistent with this diagnosis was the presence of an arachnoid cyst. A course of oral prednisone, 80 mg/day, was begun. Some return of sensory and motor function was apparent over the next 5 days. At 9 weeks she is still markedly paretic with some sensation returning to her legs and buttocks. She continues to be incontinent of feces and unable to void.

Laboratory tests including liver function studies, serum cholinesterase levels, and dibucaine number were normal. Cerebrospinal fluid analysis during the second admission was also unremarkable.

## Discussion

The complications encountered here, a cauda equina syndrome and progressive adhesive arachnoiditis, have not been reported in association with spinal anesthesia for more than 25 years.[2] Our patient initially developed total spinal anesthesia as evidenced by the rapid onset of symptoms with complete loss of somatic motor function, and the fact that the first muscle groups observed to recover were the right extraocular muscles. Although Dawkins[3] suggests that massive spinal anesthesia may follow inadvertent subarachnoid injection of an epidural dose of local anesthetic as frequently as once in 500 epidurals, even after a negative response to a test dose, there are no reports of prolonged neurologic deficits in association with such injection.[3,4] Total spinal anesthesia with smaller doses of 2% or lower concentrations of 2-chloroprocaine has occurred, and the effects have been transient.[5-7] Indeed, 3-ml volumes of 3.3% 2-chloroprocaine were used by Foldes[8] and colleagues for spinal anesthesia with good results and no neurologic sequelae.

The etiology of our patient's catastrophic complication is unclear. Although a common cause of neurologic residua after high or total spinal anesthesia is said to be spinal cord ischemia due to hypotension, our patient was not significantly hypotensive.[9] No preservatives were present in the local anesthetic solution. Antiseptic solution is unlikely to have contaminated the drug, as the preparation tray was removed from the epidural set. Since we were using a disposable epidural tray (Travenol #2D2378), a contaminant such as residual detergent or germicidal solution in a syringe is unlikely. The concentration and total amount of epinephrine used were no greater than that routinely used for spinal anesthesia. The slow, but nearly complete, recovery that our patient made was at first reassuring. The delayed appearance of the progressive neurologic symptoms described is not atypical for the development of adhesive arachnoiditis, a disorder which may take weeks, or even months, to become clearly manifest.[10]

The pH of 3% 2-chloroprocaine is between 3.3 and 3.4, which makes it the most acidic of the local anesthetic preparations, even those to which the manufacturer has added epinephrine (Pennwalt Pharmaceutical Division, Pennwalt Corporation. Data confirmed by Corning 165/2 pH meter in our laboratory). The volume of drug injected was nearly equal to the amount of cerebrospinal fluid present below the foramen magnum, i.e., 25 to 30 ml.[11] If this volume of spinal fluid were replaced by such an acidic solution, this might result in a slow return to physiologic pH. 2-Chloroprocaine may undergo some metabolism in cerebrospinal fluid by alkaline hydrolysis; pseudocholinesterase plays little role as there is almost none present in the subarachnoid space.[12] At a pH below 6.0 almost no alkaline hydrolysis occurs. It is conceivable that the acid pH greatly delayed the hydrolysis of the drug in cerebrospinal fluid while the epinephrine prevented early uptake of the agent by the blood stream, thereby delaying the usual route of elimination of the drug from the subarachnoid space. However, we would expect this to prolong the block by hours, not by weeks. Studies of isolated nerve preparations have shown 2% 2-chloroprocaine to be unassociated with significant microscopic changes.[13] Comparable studies have not been performed with 3% 2-chloroprocaine; therefore, we do not know whether the duration of exposure to this concentration plays any role in its potential toxicity. Prolonged exposure to other local anesthetics has shown no adverse effect.[9, 13]

There is a remote possibility that a chemically contaminated lot of the drug was used. We could not identify the lot number of the injected drug. We have, however, recently learned of two other prolonged courses after intrathecal injection of large volumes of 3% 2-chloroprocaine without epinephrine (personal communication). The drugs utilized in these cases were analyzed and found to be free of contaminants.

It is also possible that the 3% concentration of 2-chloroprocaine, when injected in large volumes into the subarachnoid space, is at the threshold of human toxicity. Moore[14] stated 25 years ago that the local anesthetic itself was the causative factor in the series of permanent neurologic injuries which he reviewed. In addition he noted that " . . . the only conditions under which an unusually excessive volume of local anesthetic drug might reach the subarachnoid space and/or parenchyma of the spinal cord is when it is inadvertently injected subarachnoidally while performing an epidural (peridural) or paravertebral block . . . "

Whether or not our patient's neurologic deficit is a direct toxic effect of this concentration of 2-chloroprocaine or the result of the alteration in cerebrospinal fluid pH, it is clear that extreme caution in the use of 3% 2-chloroprocaine for epidural anesthesia is warranted until laboratory data can explain this phenomenon. If this agent is to be used, we recommend a test dose of 3 ml with careful observation for 3 to 5 minutes. We then suggest that the anesthetic dose be administered in increments, rather than as a large bolus, with a few minutes between each aliquot to allow for adequate patient assessment. Regardless of the technique utilized, single injection or continuous, the anesthetist should employ every possible means to avoid the intrathecal injection of a large volume of 3% 2-chloroprocaine. If inadvertent injection occurs, spinal fluid drainage as soon as the patient's cardiovascular and respiratory status are stable might prove helpful. A course of oral steroids may prevent or lessen any persistent neurologic residua,[15] although a recent study suggests that early treatment is of little value in preventing contrast medium-induced arachnoiditis.[16] Microsurgical lysis of the adhesions remains a highly controversial therapeutic modality for advanced arachnoiditis.[17]

## REFERENCES

1. Johnson RW: Editorial, Anaesthesia 34:387-838, 1979
2. Vandam LD: Spinal anesthesia-accepted, Controversy in Anesthesiology. Edited by JE Eckenhoff. Philadelphia, WB Saunders Co, 1979, pp 11-12
3. Dawkins CJM: An analysis of the complications of extradural and caudal block. Anaesthesia 24:554-563, 1969
4. Bromage PR: Epidural Analgesia. Philadelphia, WB Saunders Co, 1978, pp 656-657
5. Allen PR, Johnson RW: Subarachnoid injection during extradural analgesia for labour using 2-chloroprocaine. Anaesthesia 34:874-876, 1979
6. Woerth SD, Bullard RJ, Alpert CC: Total spinal anesthesia, a late complication of epidural anesthesia. Anesthesiology 47: 380-381, 1977
7. Kim YI, Massa NM, Marx GF: Massive spinal block with hemicranial palsy after a "test dose" for extra dural anesthesia. Anesthesiology 43:370-372, 1975
8. Foldes FF, McNall PG: 2-Chloroprocaine: a new local anesthetic agent. Anesthesiology 13:287-296, 1952
9. Usubiaga JE: Neurologic complications following epidural anesthesia. Int Anesthesiol Clin 13:15-27, 1975
10. Greene NM: Neurological sequelae of spinal anesthesia. Anesthesiology 22:682-698, 1961
11. Collins VG: Principles of anesthesiology. Second edition. Philadelphia, Lea & Febiger, 1976, p 647
12. Foldes FF, Aven MH: The hydrolysis of procaine and 2-chloroprocaine in spinal fluid. J Pharmacol Exp Ther 105:259-265, 1952
13. Pizzolato P, Renegar OJ: Histopathological effects of prolonged exposure of nerves to local anesthetics. Anesthesiology 20:134-135, 1959
14. Moore DC: Complications of Regional Anesthesia. Springfield, IL, Charles C Thomas, 1955, p 214
15. Feldman S, Behar AJ: Effect of intrathecal hydrocortisone on advanced adhesive arachnoiditis and cerebrospinal fluid pleocytosis. Neurology 11:251-256, 1961.
16. Haughton VM, Eldevik OP, Ho KC, et al: Arachnoiditis from experimental myelography with aqueous contrast media. Spine 3:65-69, 1978
17. Johnston JDH, Matheny JB: Microscopic lysis of lumbar adhesive arachnoiditis. Spine 3:36-39, 1978

ANESTH ANALG
59:455–456, 1980

# A Guide-Wire Technique for Replacement of Swan-Ganz Catheters

**Steven Shoum, MD, Roberta C. Kahn, MD, Graziano C. Carlon, MD, and William S. Howland, MD**

The indications for use of the Swan-Ganz thermodilution catheter in the management of critically ill patients have broadened considerably since its introduction into clinical use.[1, 2] Some patients may require the placement of an indwelling catheter for several days to weeks, and since contamination, sepsis, catheter displacement, or balloon breakage may require replacement of the catheter, it is often necessary to perform a new percutaneous subclavian or internal jugular puncture for this purpose.

Many of our patients are leukopenic, thrombocytopenic, and supported with mechanical ventilation, all of which contribute to the risk of percutaneous insertion of central venous catheters. Consequently, we have adapted the familiar guide-wire technique to facilitate replacement of Swan-Ganz catheters through an already existing percutaneous site of insertion.

## Technique

With the patient in 15° head-down position and after sterile preparation the Swan-Ganz catheter is withdrawn from its position until the 20-cm mark is beyond the site of insertion (10 to 15 cm remain indwelling). The catheter is held at the site of insertion and cut just distally; blood returning through the distal lumen of the catheter identifies it for passage of a 0.64-mm diameter, 30.5-cm long guide-wire (Arrow International Inc, AW04025), which is introduced approximately one half to two thirds of its length, and the remaining catheter is withdrawn. An 18-gauge, 6.35-cm catheter is then passed over the guide wire into the vein and the guide wire removed. A 0.89-mm diameter 40-cm guide wire (18-gauge catheter, 40-cm guide wire, Arrow Percutaneous Sheath Introducer Kit AK05800) is then passed, the catheter removed, and an introducer-dilator assembly (Arrow Percutaneous Sheath Introducer Kit AK05800) is placed. Removal of the wire and dilator from the introducer now allows passage of a new Swan-Ganz catheter. After proper placement of the Swan-Ganz catheter, the introducer is withdrawn from the insertion site, and the Swan-Ganz catheter sutured to the skin. All components of this technique are illustrated in the Figure.

## Discussion

We have used this technique for approximately 25 changes of a Swan-Ganz catheter and we find it safe and rapid; it employs only one more piece of equipment than would be necessary for a new subclavian or internal jugular puncture, namely the 0.64-mm guide wire, which we also use to change 20-gauge arterial lines.

Replacement of a pulmonary arterial catheter through the same site of insertion has been described utilizing the catheter itself as a guide over which an introducer sheath is passed.[3] We have found in some instances that buckling or disruption of the end of the introducer occurs on attempted passage, and this may predispose to laceration of the vein. The thrombocytopenic patient poses our greatest concern in this instance, since hemorrhage from the subclavian or internal jugular vein may be uncontrollable.

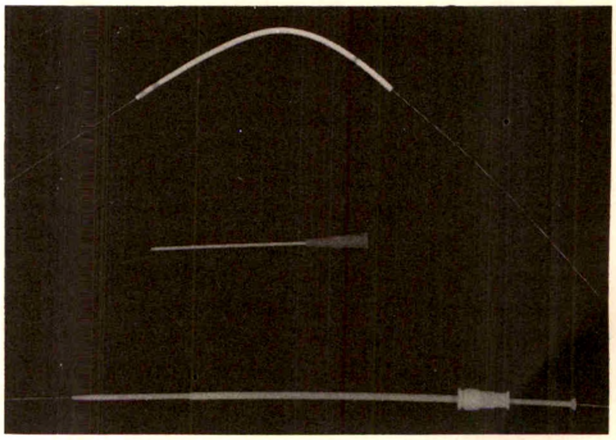


FIGURE. Components from top to bottom: (1) 0.64-mm guide-wire, passed through the distal lumen of a Swan-Ganz catheter, (2) 18-gauge catheter, and (3) 0.89-mm guide-wire within the dilator-introducer assembly.

---

Received from the Departments of Critical Care and Anesthesiology, Memorial Hospital for Cancer and Allied Diseases, 1275 York Avenue, New York, New York 10021. Accepted for publication March 1, 1980.

Reprint requests to Dr. Kahn, Department of Critical Care.

Recently the sterility of changing Swan-Ganz catheters, over the same site of insertion has been questioned.[4] The circumstances in which we replace Swan-Ganz catheters are generally limited to instances of backward migration of the catheter, balloon breakage, or obstruction of a lumen in the catheter. We are currently conducting a prospective study of the incidence of infection introduced by insertion and replacement of indwelling catheters; preliminary data in our patients fail to indicate an increased incidence of positive blood cultures obtained through Swan-Ganz catheters replaced through the same site of insertion.

In summary, replacement of an indwelling Swan-Ganz catheter with a new percutaneous cannulation of a subclavian or internal jugular vein exposes the patient to the undesirable risks associated with percutaneous cannulation. A guide-wire technique for replacing a Swan-Ganz catheter through the existing insertion site has been described. The technique avoids the necessity for repetitive percutaneous cannulation, and it is safe, rapid, and uses readily available equipment.

### REFERENCES

1. Swan HJC: The role of hemodynamic monitoring in the management of the critically ill. Crit Care Med 3:83-89, 1975
2. Shoemaker WC, Chang P, Bland R, et al: Cardiorespiratory monitoring in postoperative patients: quantitative therapeutic indices as a guide to therapy. Crit Care Med 7:243-249, 1979
3. Shaffer LJ: Sterility and repositioning of the Swan-Ganz catheter. Chest 75:743, 1979
4. Applefeld JJ, Caruthers TE, Reno DJ, et al: Assessment of the sterility of long-term cardiac catheterization using the thermodilution Swan-Ganz catheter. Chest 74:377-379. 1978

---

## High-Dose Steroid Therapy in Head Injury

While corticosteroids in standard neurosurgical dosage do not seem to influence recovery from severe head injury or elevated intracranial pressure (ICP), some reports claim that a much higher dosage is effective. A resultant hypothesis is that an abrupt increase in corticosteroid dosage in patients with severe head injury should cause a detectable reduction in ICP and in cerebral elastance within 48 hours. To test this hypothesis, 20 consecutive patients with severe head injury, 12 of whom had had surgical decompression of mass lesions, were studied. All patients were artificially ventilated and had continuous monitoring of ICP and intermittent testing of elastance by measurement of the volume-pressure response (VPR). For the first 12 hours after admission, patients received methylprednisolone, 40 mg every six hours. The dosage was then increased abruptly by giving a single dose of 2 g and 500 mg every six hours for the next 24 hours, then tapering rapidly. No significant change in ICP or VPR could be detected after 24 or 48 hours of high-dose steroid therapy. Of the 20 patients, 50% had good recovery or were moderately disabled, 15% were severely disabled or vegetative, and 35% died. There was also a high incidence of gastric hemorrhage (50%) and of hyperglycemia with glucosuria (85%). *(Gudeman SK, Miller JD, Becker DP, et al: Failure of high-dose steroid therapy to influence intracranial pressure in patients with severe head injury. J Neurosurg 51:301-306, 1979)*

ANESTH ANALG
59:457-458, 1980

# A New Head Strap

**Subhash Chander, MB, BS**

The conventional mask retainer with four straps often does not provide an airtight mask fit and fails to support the chin. This paper describes a new mask retainer with six straps that improves performance in these two areas.

## Methods and Materials

As illustrated in Fig 1, the new head strap consists of a central body and six straps. It can be made easily by cutting it out of a piece of conductive elastic sheet rubber. The recommended measurements, position, and direction of the straps are indicated in Fig 1.

The application of the strap is illustrated in Fig 2. The strap is placed under the patient's head with straps A and B superior, E and F inferior, and C and D on the sides. After induction of anesthesia, a clear airway is first obtained with or without the use of an oral or nasopharyngeal airway. In edentulous patients, the use of an oral airway provides a better shaped face for a better mask fit. The appropriate size and type of anesthetic mask with four retaining hooks is now placed on the face so that it is not pressing against the supraorbital margin. The straps are now anchored in the hooks in the following order: A and B, C and D, E and F. When fastened, straps C and D come around the angle of the mandible and gently push the soft tissues of the buccal area against the cushioned margin of the face mask and seal any gas leaks in this area. Straps E and F are crossed under the chin. This supports the chin, improves the airway and prevents any gas leaks in this area. Care should be taken that these straps do not compress the carotid vessels. When fastening, the straps should not be stretched excessively.

## Discussion

The presently available conventional mask retaining head strap (one with four straps) can be applied in one of two ways: (1) with the lower straps around the side of the face over the angles of the jaw and buccal fat area, or (2) with the lower straps crossed under the chin holding the jaw up against the face mask.

With the first method there is no support to the chin. This often causes a big leak of gases in this area, especially when the head is extended to keep a clear airway. The lack of support to the chin leaves the muscles of the floor of the mouth relaxed causing soft tissues to obstruct the airway. Also, there is no force counteracting the pull of the upper straps which pull the mask superiorly. Therefore, the mask tends to creep up above the bridge of the nose causing pressure on the medial angles of the eyes and supraorbital margin. This may result in edema of the eyelids, chemosis of the conjunctiva, pressure on the supraorbital and supratrochlear nerves, corneal injury, and possibly temporary blindness due to the acutely increased intraocular pressure.

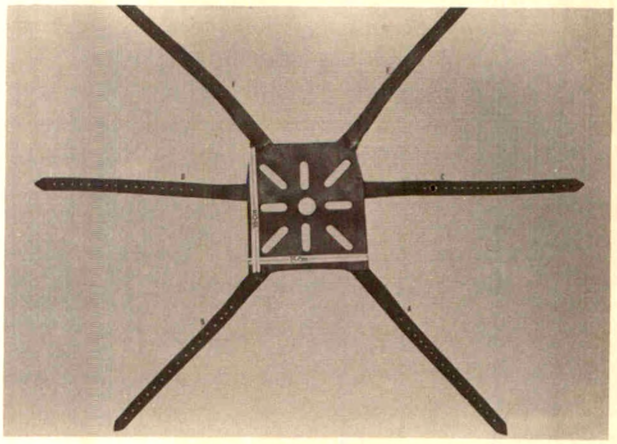


FIG 1. New head strap.

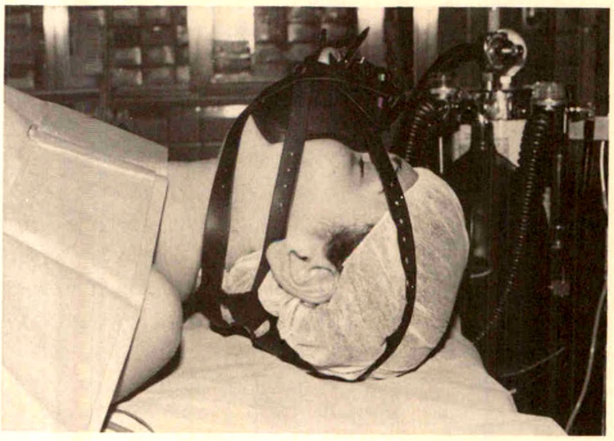


FIG 2. Method of application of head strap.

---

* Chief Resident Anesthesiologist.

Received from the Department of Anesthesiology, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11042. Accepted for publication March 6, 1980.

The chin may be supported using the conventional head strap by crossing the two lower straps under the chin. This avoids many problems of method 1 above, but in many instances leaves a gas leak in the cheek area, especially in the edentulous patient. With either method, a better fit is derived by supporting the jaw with the hand. This is tiresome for the anesthesiologist and limits his freedom to do other things (e.g., administer drugs, take blood pressure, etc) without an assistant's help.

When applied properly, the mask retainer described here provides the best possible fit of the mask in all, including edentulous patients. It supports the chin and does not let the mask creep up above the bridge of the nose, and the pulling force of the straps is distributed more uniformly over the entire head. A potential disadvantage is that in the event of vomiting, it will take slightly longer to untie this retainer as compared to the four strapped device.

---

## Adrenergic Influences on Potassium Kinetics

The role of catecholamines in the regulation of potassium homeostasis was studied in nine healthy subjects given intravenous potassium chloride (0.5 meq/kg of body weight) in the presence and absence of propranolol. Potassium infusion elevated serum potassium 0.6 ± 0.09 meq/L (mean ± SEM). Addition of propranolol augmented the rise (0.9 ± 0.05 meq/L) and prolonged the elevation in serum potassium without decreasing urinary potassium excretion. In a separate study, the same potassium load was administered with a concomitant infusion of epinephrine in five subjects. Epinephrine markedly blunted the increment in serum potassium (0.1 ± 0.06 meq/L) while reducing renal potassium excretion. Plasma aldosterone was not altered by the experimental procedures. Serum insulin fell minimally in the presence of propranolol but was unaffected by epinephrine. $\beta$-Adrenergic blockade impairs, and epinephrine enhances, extrarenal disposal of an acute potassium load. These findings suggest that in patients with impaired potassium disposal, the risk of hyperkalemia may be increased when sympathetic blockade is induced. *(Rosa RM, Silva P, Young JB, et al: Adrenergic modulation of extrarenal potassium disposal. N Engl J Med 302:431–434, 1980)*

## Simultaneous Chest Compression and Ventilation during CPR

In most patients blood flow during cardiopulmonary resuscitation (CPR) results from a rise in intrathoracic pressure rather than from direct heart compression. Intrathoracic pressure was increased by the use of positive-pressure ventilation synchronous with sternal compression in 11 arrested patients who were intubated. A computer system allowed 15- to 30-second periods of alternation between conventional CPR and "new CPR" (rate of 40/min, 60% compression duration, and simultaneous ventilation at airway pressures from 60 to 110 cm $H_2O$). The compression force was identical with the two methods. "New CPR" increased mean systolic radial artery pressure significantly from 40.6 ± 4.4 to 53.1 ± 3.9 mm Hg for 14 runs in nine patients. In 15 runs in ten patients an index of carotid flow increased with "new CPR" to 252% (range 113% to 643%) of control values. Lowering airway pressure during "new CPR" lowered flow index and arterial pressure, confirming that these increases with "new CPR" were due to higher intrathoracic pressure. Thus, increased airway pressure synchronous with sternal compression increases arterial pressure and likely blood flow during CPR in man. However, further studies of potential complications and long-term effects of "new CPR," particularly on adequacy of ventilation, are needed before clinical use of the technique. *(Chandra N, Rudikoff M, Weisfeldt ML: Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. Lancet 1:175–178, 1980)*

# letters TO THE EDITOR

## Atropine in Physostigmine Reversal of Diazepam

To the Editor:

Failure to reverse diazepam-induced sedation with a physostigmine-atropine solution as reported by Garber et al[1] should come as no surprise. The authors correctly point out that the reason for this failure may be that physostigmine may not reverse all of the central nervous system depression produced by atropine. The incorrect statement is that atropine must be used when physostigmine is used in order to avoid the unpleasant muscarinic side effects. We have had the opportunity to "arouse" patients with prolonged recovery from barbiturate, ketamine, and diazepam[2] sedation using physostigmine alone and have not seen "unpleasant" muscarinic side effects. It is interesting to note that if arousal is to occur it will usually occur about 7 minutes after the physostigmine injection.

It is our impression that the patients who receive the atropine represent examples of the central anticholinergic syndrome. We feel that reversal of diazepam-induced sedation will be more successful if physostigmine is used alone.

Denis J. Cuka, MD
*Associate Professor*
Jerry D. Edelman, MD
*Assistant Professor*
*University of Nebraska Medical Center*
*Omaha, Nebraska 68105*

REFERENCES

1. Garber JG, Ominsky AJ, Orkin FK, et al: Physostigmine-atropine solution fails to reverse diazepam sedation. Anesth Analg 59: 58-60, 1980
2. Larson GF, Hurlbert BJ, Wingard DW: Physostigmine reversal of diazepam-induced depression. Anesth Analg 56:348-351, 1977.

---

To the Editor:

In the article "Physostigmine-Atropine Solution Fails to Reverse Diazepam Sedation" by Garber et al (Anesth Analg 59:58-60, 1980), I feel the authors may have come to an erroneous conclusion based on the pharmacology of the drugs involved—specifically, the ability of the drugs used to cross the blood-brain barrier.

That the mixture of physostigmine and atropine has no analeptic effect on diazepam sedation appears valid from their experiment. However, both drugs are tertiary ammonium compounds and readily pass into the central nervous system (CNS). If physostigmine could, by a cholinomimetic effect in the CNS, block sedation induced by diazepam, then atropine could, by an anticholinergic effect in the CNS cancel this effect. Furthermore, the authors state that atropine must be used with physostigmine to avoid unpleasant muscarinic effects.

There is another choice. Glycopyrrolate, a quaternary ammonium compound that does not cross the blood-brain barrier appreciably, will block the peripheral muscarinic effects of physostigmine as effectively as atropine. This would allow the cholinomimetic effect of physostigmine to work in the CNS unopposed.

Therefore, I feel the authors have only proven that the combination of atropine and physostigmine fails to reverse diazepam sedation and not that "physostigmine does not have an analeptic effect on diazepam-induced sedation." The atropine may have blocked the effect as explained above. Perhaps the experiment should be repeated with physostigmine alone or physostigmine-glycopyrrolate in combination.

Jeffrey Belkin, MD
*Department of Anesthesiology*
*Sinai Hospital of Detroit*
*Detroit, Michigan 48235*

---

To the Editor:

The letters from Drs. Cuka and Edelman and from Dr. Belkin raise two interesting questions. Does 1 mg of atropine have a significant effect in blocking the central nervous system action of physostigmine? And, is the use of an anticholinergic agent necessary when administering physostigmine?

We are pleased that Dr. Belkin has reached the same conclusion as contained in our paper, that in fact a physostigmine-atropine mixture failed to improve psychomotor function in patients sedated with diazepam. However, whether this was caused by the opposing pharmacologic effect of atropine or the inability of physostigmine to reverse psychomotor impairment caused by diazepam cannot be answered at the present time. It does seem clear that a physostigmine-atropine mixture is highly effective in reversing scopolamine sedation despite the presence of as much as 1.5 mg of atropine in the physostigmine-atropine mixture. We are currently involved with a similar study using glycopyrrolate and hopefully a clearer answer will be forthcoming.

We appreciate Drs. Cuka and Edelman's subjective clinical view that they were able to "arouse" patients from barbiturate, ketamine, and diazepam sedation with physostigmine, but find no convincing objective controlled scientific data to support this position.

Our impression that an anticholinergic was necessary to block unpleasant muscarinic effects was confirmed in a recent study by Bidwai et al[1] in which patients in an experimental group receiving 2 mg of physostigmine alone had a 60% incidence of nausea and vomiting. Perhaps the differences observed in the incidence of side effects with physostigmine is related to the different levels of patient sedation at the time of the drug's administration.

Jeffrey G. Garber, DMD
Alan Jay Ominsky, MD
Fredrick K. Orkin, MD
*Department of Anesthesia*
*University of Pennsylvania*
*3400 Spruce Street*
*Philadelphia, Pennsylvania 19104*

REFERENCE

1. Bidwai A, Stanley TG, Rogers C, et al: Reversal of diazepam-induced postanesthetic somnolence with physostigmine. Anesthesiology 51:256–259, 1979

---

## Correction

To the Editor:

In my Letter to the Editor (Anesth Analg 58:158–159, 1979), written in response to the Letter by Mirakhur and Dundee about Baraka's article on "Gastric Acidity and Glycopyrrolate Premedication" (Anesth Analg 56: 642–645, 1977), I made two serious mistakes, and if one reads the letter as it appears, the mistakes disprove my argument. In discussing the fact that the dosage of glycopyrrolate utilized by Mirakhur and Dundee (0.2 mg) was simply insufficient to achieve the desired elevation of pH, I intended to state, "that such is the case was surely substantiated by the data presented by Baraka et al, which indicated that 0.4 mg of *glycopyrrolate* would elevate the pH of gastric contents to above 2.5 in 82% of the parturients *if* the glycopyrrolate was administered more than 60 minutes prior to the induction of anesthesia." In the published letter, the word atropine is erroneously substituted for glycopyrrolate.

Later, I meant to state that "in short, the findings of Mirakhur and Dundee that *0.2* mg of glycopyrrolate is indistinguishable from 1 mg of atropine regarding the effects on pH of gastric contents, is simply a result of inadequate dosage, and does not indicate that glycopyrrolate, given in adequate dosage and a sufficient time prior to the induction of anesthesia (or sampling of gastric juice), cannot raise the gastric pH above 2.5 in a clinically significant percentage of cases." In the published letter, the dosage for glycopyrrolate erroneously reads 2 mg (a 10-fold increase in the dosage).

Alon P. Winnie, MD
*Professor and Chairman*
*Department of Anesthesiology*
*University of Illinois*
*Medical Center*
*Chicago, Illinois 60612*

---

## Erratum

In the paper "Anesthesiology and Its Publications" by Nicholas M. Greene (*Anesth Analg* 59:1-2, 1980) the first date of publication of *Anesthésie et Analgésie* was erroneously given as 1944. The correct date is 1935. Publication was suspended between 1941 and 1944.

# book REVIEWS

### **Pain—Association for Research in Nervous and Mental Disease, Volume 58,** edited by J. J. Bonica, New York, Raven Press, 1979, 420 pp, $25.00.

This book contains the papers presented and discussions held during the 58th Annual Meeting of the Association for Research in Nervous and Mental Diseases (ARNMD) which was devoted to pain. The contributors are all internationally known scientists, and the papers were edited by Dr. Bonica, a unique pioneer in the field of pain research.

The volume is divided into two parts. The first part concerns basic aspects of nociception and pain including anatomic and physiologic aspects of pain perception, psychological and psychiatric aspects of pain, and modulation and measurement of pain. It appears that this information is up to date and helpful for comprehension of pathways and functional characteristics of nociceptive central transmission and modulations. The second part concerns clinical aspects of pain including the role of the psychiatrist, headaches, central mechanisms of chronic pain which is explained by surgical interruptions, causalgia, cancer pain, and low back pain.

The authors try to approach the reality of treatments from scientific rationale as well as philosophic considerations. The book offers a well balanced choice of topics and discussions from which unbiased judgments may be formed. Reading through this book, I did not come away with the impression, as one author stated, that many who have suffered from chronic pain do not have any relevant lesion and that chronic pain is primarily determined by psychological causes.

The entire book is informative, and it includes rather enjoyable general discussions. The authors speak with clarity and authority, and yet I feel an uncertainty and anxiety toward the gaps yet to be filled between our daily treatment and scientific facts, as well as proposed hypotheses. This uncertainty, of course, creates a desire to know more about the rapidly evolving area of pain research; the book is stimulating reading.

Kasumi Arakawa, MD
Professor and Chairman
Department of Anesthesiology
University of Kansas
Medical Center
Kansas City, KA

### **Hemotherapy in Trauma & Surgery,** by The Committee on Workshops of the American Association of Blood Banks. Washington, American Association of Blood Banks, 1979, 88 pp, $10.00.

### **Platelet Physiology & Transfusion,** by The Committee on Workshops of the American Association of Blood Banks. Washington, American Association of Blood Banks, 1978, 92 pp, $15.00.

These are multiauthored texts which contain the proceedings of technical workshops that were presented at the 1978 and 1979 Annual Meetings of the American Association of Blood Banks. Several workshops are presented at each yearly meeting of the American Association of Blood Banks as a means of presenting new developments in the practice of blood banking. These workshops are subsequently published and made available to blood bankers and those in related medical fields. Both texts are informative not only to blood bankers but to those in other specialties including anesthesiology and surgery.

The 1978 workshop, Platelet Physiology and Transfusion, was written by experts familiar with the rapidly changing field of platelet storage and transfusion. The seven chapters deal with selection of donors, metabolism and function of platelets during storage, platelet production and inventory management, and future research application. Of particular interest are chapters dealing with platelet transfusion in patients with cancer, platelet function and transfusion during surgery, and management of patients refractory to random donor platelet transfusions. The chapter dealing with platelet function and transfusion in surgery written by Marcus B. Simpson, MD, Director of the Walter Reed Medical Center Blood Bank, is an excellent discussion of platelet bleeding disorders in the surgical patient and includes clinical and laboratory evaluation and management of these disorders. This chapter includes a discussion of several specific platelet disorders that develop in the surgical patient; some of these are disorders related to cardiopulmonary bypass (which Simpson notes rarely require platelet transfusion), massive transfusion, use of the intraaortic balloon, disseminated intravascular coagulopathy, hepatic disease, and Von Willebrand's disease.

Hemotherapy in Trauma and Surgery, presented in 1979, was intended to inform blood bankers about recent developments in transfusion therapy that have occurred outside of the blood bank, in particular, the operating room. Like the previous book this text contains material of interest to the anesthesiologist and surgeon. Again, it is a multiauthored text containing seven chapters dealing with hemorrhagic shock and its various transfusion-related problems. The first chapter is a detailed discussion of the pathophysiology of hemorrhagic shock and is followed by two chapters dealing with coagulation and problems of blood and blood component replacement during shock states. These two chapters represent the only weak area of the book since their discussion of the various problems is somewhat superficial in nature. Other chapters cover the various devices and methods used for intraoperative blood salvage as well as red-cell salvage during open-heart surgery. There is also an excellent chapter covering the practical aspects of blood transfusion such as the use of the type and screen and the abbreviated crossmatch in the emergency transfusion situation. Of particular interest is the chapter written by Charles G. Zaroulis of the Memorial Sloan-Kettering Institute for Cancer Research presenting evidence claiming to substantiate the use of high 2,3-DPG red-cells in transfusion therapy.

Stephen M. Brzica, MD
Associate Professor
of Anesthesia
University of Minnesota
School of Medicine
St. Paul, MN

---

## Anesthesia & Neurosurgery, by J. E. Cottrell and H. Turndorf, St. Louis, CV Mosby Co, 1979, 433 pp, $47.50.

The goal of this book, as stated in the preface, is to incorporate an organized basic science curriculum with the clinical practice of neuroanesthesia. Cottrell and Turndorf's text comes closer to realizing this objective than any of the other neurosurgical anesthesia texts currently available.

The strength of the book lies in the editors' selection of contributors, who represent all disciplines related to neurosurgical anesthesia and many different institutions. Controversial topics are with few exceptions presented in a well balanced discussion, not just reflecting the views of a single individual or institution. A notable exception to this is the statement that the Doppler and right atrial catheter should be used in all neurosurgical cases because air embolism can occur in the lateral, supine, and prone as well as sitting positions.

The basic science in the book is excellent. Cerebral blood flow, metabolism, neurophysiologic evaluation and monitoring, cerebrospinal fluid mechanisms, and intracranial pressure-volume relationships are well covered. The material is presented clearly with ample illustrations. The clinical areas are likewise well presented, with a significant emphasis placed on head injuries and their peripheral sequelae. There are interesting sections on neuroradiologic diagnostic studies, anesthesia for neuroradiologic procedures, and brain death. The chapter on induced hypotension is particularly well written. The time lag between writing and publication is especially evident in some chapters; for example, the chapter on barbiturate protection of the ischemic brain has references up to 1978, but much work has been published since then.

A problem arising from the large number of contributors is repetition among the chapters. However, this does enable a reader to review a topic in one or two chapters without having to skip throughout the text and makes the chapters independent. A more serious shortcoming is the omission of several important areas of neuroanesthesia. For example, coverage of pediatric neuroanesthesia is limited to the chapters on anesthesia for neuroradiologic procedures and management of severe head injury; there is no consideration of Reye's syndrome. Also, the coverage of cerebrovascular disease is limited. There is no discussion of the anesthetic management of intracranial aneurysms or the monitoring of patients undergoing carotid endarterectomy.

Despite these shortcomings, I recommend this book to all anesthesiologists, and especially those caring for neurosurgical patients. The anesthesia resident will have an excellent presentation of basic neuroscience and approach to some clinical problems. The practitioner will have in one place a text that will detail the advances which have been made in intracranial pressure monitoring. The academician will have a text that discusses basic concepts of neuroanesthesia from many viewpoints and hence, may provide useful teaching tools. Neurosurgeons, neurologists, and critical care specialists will also find the book to be of interest and benefit in their practice.

Robert D. McKay, MD
Assistant Professor
of Anesthesiology
Director of Neurosurgical
Anesthesia
University of Alabama
in Birmingham
Birmingham, AL

---

## Der Einfluss von Anaesthetica auf die Kontraktionsdynamik des Herzens, by K. J. Fischer. New York, Springer-Verlag, 1979, 278 pp, $43.50. Zur Herzwirkung von Inhalationsanaesthetica, by H. P. Siepmann, New York, Springer-Verlag, 1979, 66 pp, $21.80.

These two monographs are discussed together since some of their subject matter overlaps.

Dr Fischer discusses a large body of experimental work with a heart-lung preparation to test a variety of anesthetics. In the introduction, he rightly discusses the difficulties in transposing findings on experimental preparations to the intact human body. The author also introduces the concept of a "cardiac therapeutic index" (calculated from the ratio of $ED_{25}$/MAC, with $ED_{25}$ being the concentration that reduces left ventricular $dP/dt_{max}$ by 25%), a measurement which still needs to be proven useful. Dr Fischer then establishes a hierarchy of negative inotropic effects of anesthetic agents; this hierarchy is similar to American findings.

Dr Siepmann, in his much shorter

monograph, uses a papillary muscle preparation to investigate only two agents. As has been shown by others, he indicates that enflurane appears, in general, to be less of a depressant than halothane in equi-anesthetic doses.

It must be recalled that both of the experimental preparations are deprived of compensatory physiologic mechanisms and any transposal into clinical life must take this into account.

The bibliographies are excellent, as are format and makeup. The price is high ($43.50 for Dr Fischer's book). That, as well as the fact that the books are written in German and predominantly reconfirm the work of others, will make them only moderately popular in English-speaking countries.

Kurt F. Schmidt, MD
Professor and Chairman
Department of Anesthesiology
Tufts-New England
Medical Center
Boston, MA

## The Control of Chronic Pain, Current Topics in Anaesthesia, Volume 2, by S. Lipton, Chicago, Year Book Medical Publishers, 1979, 134 pp.

This monograph is one of the Current Topics series, a set of reviews designed to winnow the relevant new information on a given subject and present it concisely and clearly. This volume, written by a British pain clinic director who is thoroughly familiar with his subject, is indeed concise and clear.

The book begins with a discussion of the neurophysiology of sensory mechanisms, and in this rapidly advancing area of research, the book is inevitably out of date. However, the practicing specialist in anesthesia will find much that is new and will find it brought together in a comprehensive total picture.

When the author discusses the management of particular pain syndromes, he writes with more authority. But here the requirement of brevity prevents him from presenting a critical assessment of some methods of treatment, and the reader may become unduly optimistic about their value. Facet block and nerve blocks, in general, would have benefited from longer discussion.

The chapter on nerve blocks will attract the anesthesiologist most. The descriptions of technique are too brief to be used as "how-to" guides, and these might as well have been omitted. Anesthesia specialists are frequently called upon to perform blocks; they can easily find technical descriptions, but an orderly, up-to-date discussion of the indications for (and limitations of) specific nerve blocks in specific pain syndromes still does not exist. This book has missed an opportunity to provide it.

This is a useful introductory book for the anesthesiologist who is contemplating pain relief work in his practice. Because it is both brief and comprehensive, it would be extremely useful for residents and medical students rotating through a pain clinic service.

Kathleen M. Wood, MD
Associate Professor
of Anesthesiology
Clinical Coordinator
Pain Clinic
University of Colorado
Health Sciences Center
Denver, CO

## BOOK NOTES

## Clinical and Resuscitative Data, Second Edition. by R.P.H. Dunnill, M. P. Colvin, and B. E. Crawley, St. Louis, Blackwell Scientific Publications, 1980, 185 pp, $15.75.

This is a pocket-sized (coat, not shirt) handbook intended to make available the type of information needed in emergency situations. The data, formulae, conversion tables, normal values, nomograms, and graphs are organized and thumb-indexed for speedy access. Considerable effort to include American names for drugs is apparent, but terminology, syntax and spelling is definitely United Kingdom. American translations and equivalents are not invariably included, which may limit the usefulness of this compendium among physicians familiar only with United States terminology.

## Key Words in Anesthesiology, Second Edition. by N. M. Greene. Baltimore, Williams & Wilkins, 1980, 57 pp, $6.95.

Although the title of this second edition has been shortened, the first edition title *Key Words and Cross References for Indexing and Standardization of Nomenclature in Anesthesiology* adequately describes the contents and intent of this publication.

The need for standardization of terminology is readily apparent, and the listing of key words will allow standardization of indexing in computers or in one's personal files.

This revision is a very significant contribution to the anesthesia literature.

## BOOKS RECEIVED

**Trends in Intravenous Anesthesia,** edited by J. A. Aldrete and T. H. Stanley. Chicago, Year Book Medical Publishers, 1980, 525 pp, $42.95.

**Analytical Procedures for Therapeutic Drug Monitoring and Emergency Toxicology,** by R. C. Baselt. Davis, CA, Biomedical Publications, 1980, 316 pp, $35.00.

**Drugs and the Elderly,** edited by J. Crooks and I. H. Stevenson. Baltimore, University Park Press, 1979, 304 pp.

**Disaster Medicine—Types and Events of Disaster Organization in Various Disaster Situations, Volume I,** edited by R. Frey and P. Safar, Secaucus, NJ, Springer-Verlag, 1980, 355 pp, $46.50.

**General Anaesthesia, Fourth Edition, Volumes I and II,** by T. C. Gray, J. F. Nunn, and J. E. Utting. Woburn, MA, Butterworths Publishers, 1980, 905 pp. $89.95 each/$175.00 set.

**Sedation, Local and General Anesthesia in Dentistry, Third Edition,** by N. B. Jorgenson and J. Hayden. Philadelphia, Lea & Febiger, 1980, 299 pp, $27.50.

**Pharmacology of Ganglionic Transmission, Volume 53,** edited by D. A. Kharkevich, Secaucus, NJ, Springer-Verlag, 1980, 531 pp, $134.75.

**Neurotransmitters and Drugs,** by Z. L. Kruk and C. J. Pycock. Baltimore, University Park Press, 1979, 176 pp.

**The Human Cardiovascular System,** by J. T. Shepherd and P. M. Vanhoutte. New York, Raven Press, 1979, 351 pp, $14.95.

---

## Aspiration of Gastric Contents with pH Greater Than 2.5

The effect on the lungs of aspiration of gastric contents at a pH value greater than 2.5 was studied in anesthetized dogs. Experimental solutions were administered into the lungs at a dose of 2 ml/kg. Animals were divided into five groups: group 1 ($n = 13$) received saline at a pH of 5.9; group 2 ($n = 8$) received hydrochloric acid (HCl) at a pH of 1.8; group 3 ($n = 9$) received gastric contents containing small food particles at a pH of 5.9; group 4 ($n = 6$) received gastric contents containing food particles at a pH of 1.8; group 5 ($n = 6$) received gastric contents at a pH of 5.9 from which food particles had been filtered. Arterial blood gas tension, fractional intrapulmonary shunt, and blood pressure were measured at intervals for 48 hours. Animals that received gastric contents at a pH of 5.9 had reductions in arterial oxygenation and increases in intrapulmonary shunting that were significantly greater than those of animals receiving saline, and were as severe as those of animals receiving HCl at a pH of 1.8. If food particles were in the aspirate, hypercapnia and acidosis were also noted. There was pneumonitis in lung sections taken from animals in groups 2, 3, and 4, but not in groups 1 and 5. These findings contradict the common belief that aspiration of gastric contents at a pH greater than 2.5 is normally benign. *(Schwartz DJ, Wynne JW, Gibbs CP: The pulmonary consequences of aspiration of gastric contents at pH values greater than 2.5. Am Rev Respir Dis 121:119–126, 1980)*

## Artificial Surfactant in Hyaline-Membrane Disease

Ten preterm infants severely ill with hyaline-membrane disease (HMD) were given artificial surfactant endotracheally. Lyophilized artificial surfactant was suspended in saline, and about 10 ml of this fluid was instilled into the endotracheal tube. Oxygenation and alveolar-arterial oxygen gradients improved, the levels of inspired oxygen and peak respirator pressure could be reduced, and many of the radiologic abnormalities resolved. Acidosis and systemic hypotension were also reversed. In nine infants a patent ductus arteriosus became evident after recovery from HMD, necessitating further assisted ventilation. Eight infants survived, including five of six with birth weight less than 1500 g; two died of unrelated causes. Postnatal tracheal instillation of artificial surfactant may prove a useful treatment for severe HMD. These preliminary observations are viewed as indicating further clinical studies. The long-term effects of this treatment have not been studied. *(Fujiwara T, Maeta H, Chida S, et al: Artificial surfactant therapy in hyaline-membrane disease. Lancet 1:55–59, 1980)*

# A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

## Editorial Policies

Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

**Types of materials.** The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

**Peer review.** All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

**Legal and ethical considerations.** Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

**Editing.** All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

## Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

**Title Page.** The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

**Abstract and Key Words.** The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Define all abbreviations except those approved by the International System of Units.

*Key (indexing) terms.* Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract.

**Text.** The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

*Introduction.* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods.* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

*Results.* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

*Discussion.* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**References.** (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus.* Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus.* Consult the "List of Journals Indexed," printed annually in the January issue of *Index Medicus.*

Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

References must be verified by the author(s) against the original documents.

Examples of correct forms:

*Journal*

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

*Books and Other Monographs*

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

**Tables.** Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, #, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

Omit internal horizontal and vertical rules.

Cite each table in the text in consecutive order.

If you use data from another published or unpublished source, obtain permission and acknowledge fully.

The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

**Illustrations.** Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of *original* drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 12.7 by 17.3 cm (5 by 7 in) but no larger than 20.3 by 25.4 cm (8 by 10 in). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them using paper clips. Do not bend figures.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with background.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, *regardless of authorship or publisher,* except for documents in the public domain.

For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Some journals publish illustrations in color only if the author pays for the extra cost.

**Legends for Illustrations.** Type legends for illustrations double spaced, starting on a separate page with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

**Abbreviations.** Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

**THE MOUNT SINAI
MEDICAL CENTER, N.Y.**

DEPARTMENT OF ANESTHESIOLOGY
NEW FACULTY POSITION

Applications are invited from suitably qualified individuals for the above position.

Candidates should have an MD degree and have had previous training in scientific research in pharmacology, physiology or neuro-sciences. Preference will be given to candidates with an additional advanced degree.

In addition to engaging in research, the successful candidate will be required to participate in the teaching program in the basic sciences for Anesthesiology and for the resident house staff in training.

Faculty rank will be granted according to qualification. The opportunity exists for a joint appointment in Basic Science Department. An Anesthesiologist will be permitted limited private practice and supplemental income under aegis of the institution's Medical Service Plan. Applications and C.V. should be sent to: David C.C. Stark, M.D., Professor & Chairman, Department of Anesthesiology,

**THE MOUNT SINAI MEDICAL CENTER**
Annenberg Bldg., 7-52
One Gustave L. Levy Place, New York, N.Y. 10029

An Equal Opportunity Employer M/F

## *I.A.R.S. 1979 REVIEW COURSES*

Booklet containing 14 Review Course Lectures given at 53rd Congress in March of 1979 is available from I.A.R.S. Cleveland business office at $5.00 per copy. Supply is limited and orders will be filled on basis of receipt date of order. Make checks payable to International Anesthesia Research Society and send with order.

## ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA, effective

______________________________

______________________________

**From**—(Current or former address)

______________________________

Street Address

______________________________

City, State, Zip Code

**Important: Show your name and address exactly as your Journal is now addressed.**

______________________________

**To**—(New Address)

______________________________

Street Address

______________________________

City, State, Zip Code

______________________________

Print Your Name

# classified
# ADVERTISING

**SOUTH TEXAS ANESTHESIOLOGIST:**
Seeks associate who would like to semi-retire. Small hospital with modern equipment and good CME Program. Few emergencies. Practice is located in lower Rio Grande Valley. Climate is similar to that of Miami Beach. South Padre Island is approximately forty-five minute drive from the hospital. Minimal malpractice premiums and no state income tax. For further details, write to Box 6-80-A, % IARS.

**ANESTHESIOLOGIST:**
Wanted to join 11 man group in Upstate New York. Prefer someone completing residency or recently trained. Pediatric experience an asset. All corporate benefits. Send full CV with initial reply to Box 6-80-G, c/o IARS.

**ANESTHESIOLOGIST:**
Board certified, 35, US grad—university and private practice experience—seeks position in quality private practice setting. Prefer position in growing anesthesia department. Trained in all aspects of anesthesia including OB and cardiac. Willing to assume directorship if desired. Reply to Box 6-80-C, % IARS.

**ANESTHESIOLOGIST:**
FMG, 33, board eligible, passed Part I. Currently practicing in a university affiliated hospital. Interested in private practice group/fee for service, no geographical preference. Wide experience in all fields of anesthesia. FLEX, MA, NY and FLA licenses. Reply to Box 6-80-E, % IARS.

**MISSOURI**
Anesthesiologist wanted to join private group practice. 400-bed hospital with all specialties except open heart; little OB. Town of 100,000 with good schools, close airport, and good recreation. Excellent starting income, fringes, and potential. Reply to Box 7-79-A, c/o I.A.R.S.

**ANESTHESIOLOGY—**
3 year approved Program. All types of Anesthesia—including open heart, inhalation therapy. University affiliated. Please write to: Paul J. Ditmyer, M.D., Chairman; Department of Anesthesiology; The Toledo Hospital; 2142 N. Cove Boulevard; Toledo, Ohio 43606.

**ANESTHESIOLOGIST—UNIQUE FREE TIME:**
Southeastern North Carolina corporate practice involves supervision of C.R.N.A.'s and some respiratory and intensive care. 272-bed acute care hospital runs 4 O.R.'s with anesthesia. Join one anesthesiologist. Full Partnership 1-2 years. Average income; above average time off—up to 26 weeks a year! Completion AMA approved medical school and residency is required. Contact: Glenn C. Parrish, M.D., % Lumberton Anesthesia Associates, PA, 2802 Rowland Avenue, Lumberton, N.C. 28358. Tele: (919) 738-8154.

**FLORIDA:**
Position available for Anesthesiologist to direct Department of Anesthesia which consists of 5 Anesthesiologists and 6 CRNAs in a 350-bed rapidly expanding hospital which is the Regional Center for Neo-natology, complicated obstetrics and progressing toward doing open-heart procedures in the future. Candidate must be board certified with wide experience in the above fields. Please forward applications with Curriculum Vitae to: 301 Broadway, Suite 116, Riviera Beach, Florida 33404.

**ANESTHESIOLOGIST WANTED:**
(OB/GYN Hosp.)—SUN BELT AREA To join 5 Anesthesiologist—9 CRNA group private hospital—7000+ Private Deliveries/year. 6000+ GYN procedures/year. Excellent opportunity for research. Excellent fringe benefits and working conditions. Write: E. Theriot, M.D., Dept. of Anesthesia, Woman's Hospital, 9050 Airline Highway, Baton Rouge, Louisiana 70815.

**ANESTHESIOLOGIST NEEDED AT ALL ACADEMIC LEVELS:**
Must be Board Certified/Eligible. Duties include patient care, resident and medical student teaching and research. Positions available at the University of Missouri Medical Center Hospital and the Harry S. Truman Memorial Veterans Hospital. Interested applicants send a curriculum vitae to: G. W. N. Eggers, Jr., M.D., Professor and Chairman, Department of Anesthesiology, University of Missouri—Columbia School of Medicine, Columbia, Missouri 65212.

**ANESTHESIOLOGIST WANTED:**
To join 135 physician, multi-specialty group with an adjacent 430-bed hospital. New Clinic building recently completed. Gunderson Clinic, Ltd., is in a progressive community with expanding university and private college. Population 50,000. Cultural and recreational facilities. Beautiful setting; good schools. Excellent pension program, no investment required. Service organization. Write: J. Michael Hartigan, M.D., Chairman, Personnel Committee, Gunderson Clinic, Ltd., 1836 South Avenue, La Crosse, WI 54601.

**OBSTETRIC ANESTHESIA FELLOWSHIPS OR SPECIALTY TRAINING:**
Currently available. Approved 1 year program. High Risk Perinatal Center. New Hospital. Clinical and laboratory (animal) research stressed. Includes teaching and clinical experience (exclusively obstetric anesthesia and perinatal care). Walter U. Brown, Jr., M.D., Director of Obstetric Anesthesia, Vanderbilt University Medical Center, 1161 21st Avenue, South, Nashville, Tennessee 37232.

**F.M.G., 44, F.F.A.R.C.S.**
Flex eligible. Presently in teaching hospital in Canada. Seeks position—university or private. Reply to Box 6-80-B, % IARS.

# classified ADVERTISING

### OHIO ANESTHESIOLOGIST—

Position presently available in group comprising M.D.'s and CRNA's in 500 bed hospital with all specialities except open heart. Call or send curriculum to John Biggins, M.D., Dept. of Anesthesia, Trumbull Memorial Hospital, Warren, Ohio 44483. (216) 841-9230.

### CRITICAL CARE FELLOWSHIP

Our 300-bed Harvard affiliated teaching hospital has a position available from July 1, 1980 to June 30, 1981 for PGY 4-5 in multi-disciplinary ICU environment. Exposure to all areas of intensive care medicine including invasive and non-invasive monitoring, hyperalimentation, pulmonary care, etc. Specialty alignment not critical but anesthesia experience preferred. Reply to A. Dalal, M.D., Mt. Auburn Hospital, 330 Mt. Auburn Street, Cambridge, MA 02138. Tel: (617) 354-7260. An Equal Opportunity Employer.

### UNIVERSITY OF SOUTH FLORIDA

Chairperson, Department of Anesthesiology, College of Medicine, Tampa. Applicants should be Board Certified, should be capable and experienced in teaching, research and clinical care, and should have leadership and administrative skills appropriate to the development of a new department. Interested candidates should submit inquiries and curricula vitae to Anthony Reading, M.D., Chairman, Anesthesiology Search Committee, Box 14, USF College of Medicine, 12901 N. 30th Street, Tampa, Florida 33612. The University of South Florida is an Equal Opportunity Employer.

### MARYLAND:

The Maryland Institute for Emergency Medical Services Systems is seeking staff anesthesiologists with an interest and/or experience in critical care, trauma anesthesia and/or neuro-surgical anesthesia/critical care. MIEMSS is the 85 bed clinical center for trauma care and research in the State of Maryland. Teaching and research opportunities in a multidisciplinary setting are available. Salary negotiable, liberal fringe benefits. Send curriculum vitae to: Peter Chodoff, M.D., M.P.H., Chief, Critical Care/Anesthesia, Maryland Institute for Emergency Medical Services Systems, Baltimore, Maryland 21201

### CRITICAL CARE FELLOWSHIP:

One year fellowship in critical care for physicians who are board eligible in medicine or anesthesia. Rotation offered in anesthesia, hyperbaric medicine, infectious disease, trauma resuscitation/anesthesia, psychiatry, and computer applications. Competitive salary, opportunities for basic and clinical research available. Send curriculum vitae to Peter Chodoff, M.D., M.P.H., Chief, Critical Care/Anesthesia, Maryland Institute for Emergency Medical Services Systems, 22 S. Greene St., Baltimore, Md. 21201.

### ANESTHESIOLOGIST:

FMG board eligible. Has FLEX and N.Y. license. Available July 1980. Trained in university hospitals. Experienced in all kinds of anesthesia. Will consider all locations. Currently Chief Resident. Reply to Box 6-80-F, % IARS.

### ANESTHESIOLOGIST:

36, F.M.G., board eligible, university trained, diverse clinical experience, seeking group practice. Reply to Box 6-80-D, % IARS.

### PEDIATRIC ANESTHESIOLOGY RESIDENCY

Childrens Hospital of Los Angeles has advanced clinical program for residents at the second and third year level of training. Also accepting applications from practicing anesthesiologists who wish to update their knowledge and proficiency. Positions available from 2 months to 1 year. Specialized year approved by the AMA. For further details contact:

George B. Lewis, Jr., MD
Head, Division of Anesthesiology
Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, CA 90027
Phone (213) 662-1708

*Rates for classified advertising: $3.00 per line, minimum 5 lines; box number ads $3.50 per line. Classified display rates on request. Copy deadline 6 weeks prior to publication. Do not submit payment with order; invoices will be sent for payment prior to publication. Ad copy, subject to acceptance by publisher, should be mailed to: Anesthesia and Analgesia, 3645 Warrensville Center Rd., Cleveland, OH 44122.*

# INDEX OF ADVERTISERS

Ayerst Laboratories—*Fluothane®* . . . . . (12, (13), (14)

Breon Laboratories Inc.—*Marcaine* . . . . . (18), (19)

Classified Advertising . . . . . (24, (25)

Endo Laboratories—*Narcan®* . . . . . (4), (5), (6)

Grune & Stratton-Div. of HBJ—*Books* . . . . . (17)

K & G Healthcare Industries, Inc.—*Nicholes II Filter* . . . . . Cover 3

La Barge, Inc.—*MON-A-THERM* . . . . . Cover 2

The Mount Sinai Medical Center—*Employment Opportunity* . . . . . (23)

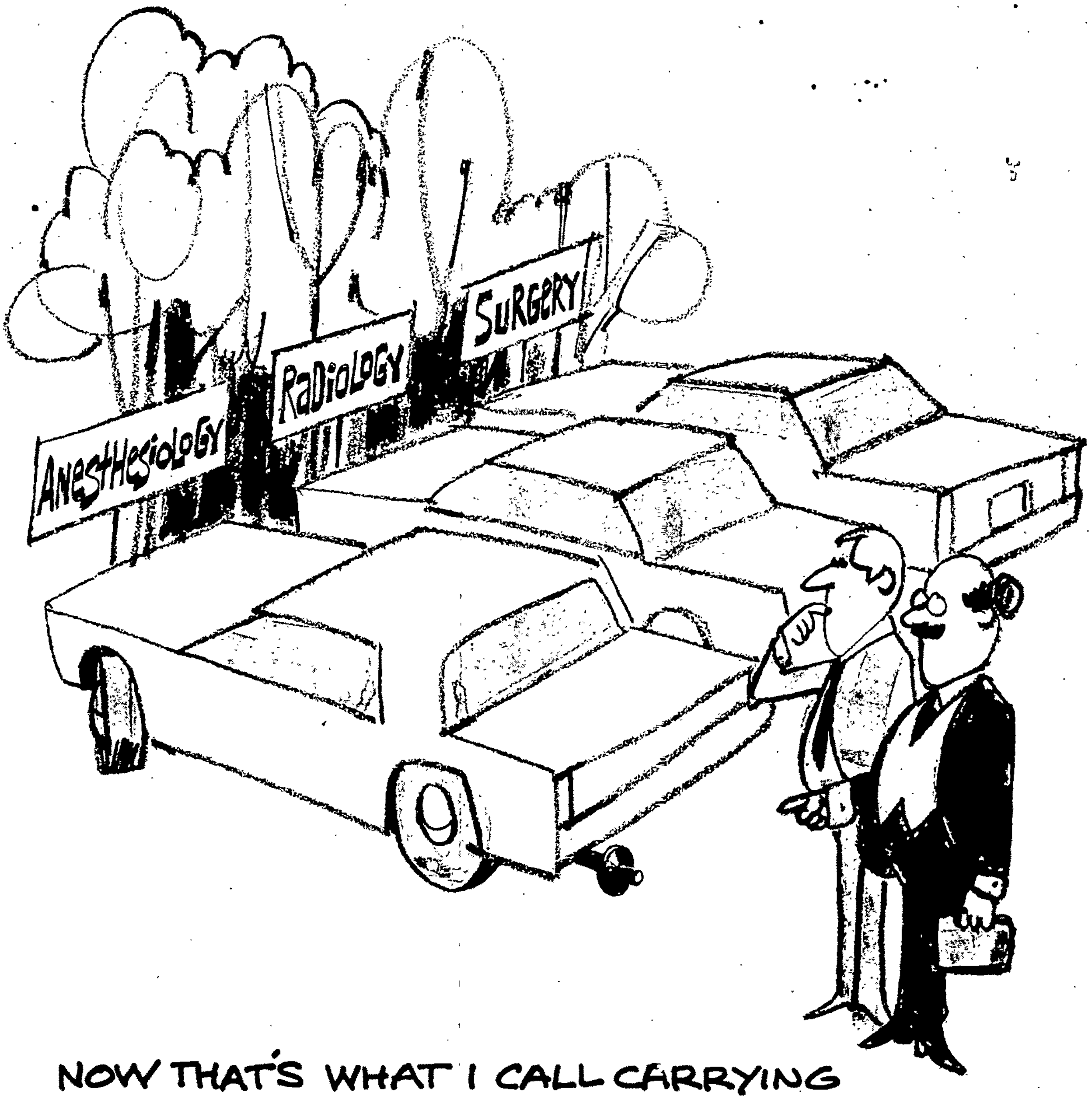
NASCO—*Spinal Injection Simulator* . . . . . (15)

NDM Corporation—*NDM Electrodes* . . . . . (7)

North American Drager—*Anesthesia Products* . . . . . (11)

Physio-Control Corporation—CMS 6000 . . . . . Cover 4

Roche Laboratories—*Valium Injectable* . . . . . (8), (9), (10)



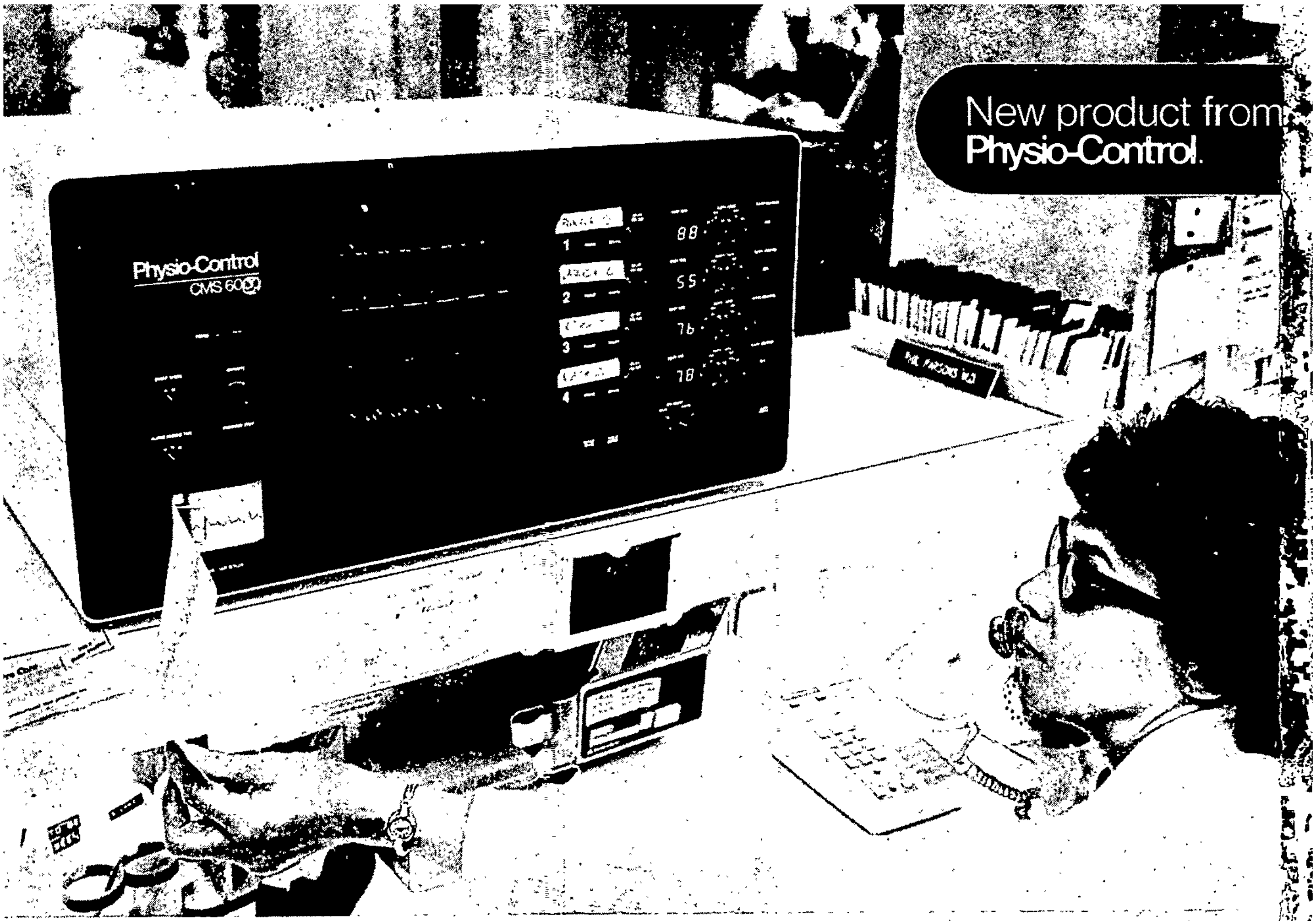
NOW THAT'S WHAT I CALL CARRYING INFECTION CONTROL JUST A LITTLE TOO FAR.

**NICHOLES-99**
VIRAL-BACTERIAL RETENTIVE FILTER

**NICHOLES II**™
THE 2nd GENERATION

Reprints of this ad available upon request, K & G Healthcare Industries, Inc. 5373 N.W. 36th Street,
Miami Springs, Florida 33166 (305) 371-3632

© K&G Healthcare, Inc. 1980



# Now! A common-sense monitoring system that's flexible, functional, reliable and affordable!

Presenting the all-new Physio-Control CMS 6000—the common-sense four-bed central ECG monitoring system. We designed it specifically for the busy Emergency Department or Recovery Room. It's also ideal for the small-hospital CCU or ICU.

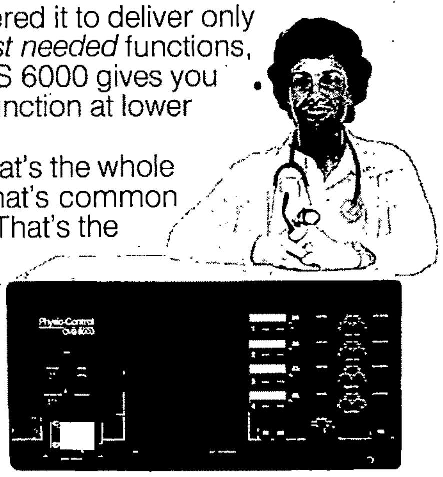
FUNCTIONAL—Four-channel cardioscope with freeze channel and recorder. Digital rate meters with high and low alarm limits.

FLEXIBLE—Use with portable Lifepak® 6 monitors as hardwired bedside monitors. Or all channels can be telemetry. Or any combination.

RELIABLE—The CMS is engineered and built with thoroughly-proven, highly-reliable electronic components. And the system is backed by Physio-Control's own nationwide factory service team.

AFFORDABLE—Because we engineered it to deliver only the *most needed* functions, the CMS 6000 gives you more function at lower cost.

That's the whole idea. That's common sense. That's the CMS 6000.



The new CMS 6000
from **Physio-Control**

---

**Physio-Control** is the world leader in acute cardiac care systems. 11811 Willows Road, Redmond, Washington 98052
(206) 881-4000/U.S. Telex: 32-0268, International Telex: 32-0166. Lifepak and Physio-Control are registered trademarks.